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 cannabinoides en el tratamiento del dolor crónico en pacientes con cáncer

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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; Cancer pain.

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**INTRODUCTION**

The use of cannabis for medicinal purposes is longstanding, as this plant has been used for therapeutic purposes for over 4000 years. However, cannabis has a high risk profile and its use for medicinal purposes is highly controversial, even for therapeutic reasons. 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. The spectrum of substances classified as CM includes: 1) Phytocannabinoids, which are found in cannabis herb and resins. The main cannabinoids are Tetrahydrocannabinol (THC) and Cannabidiol (CBD); 1) 2) Purified cannabinoids that originate from cannabis extracts (e.g. Nabiximols and purified Cannabidiol); and 3) Synthetic cannabinoids e.g. Dronabinol and Nabilone. 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. CBD has shown some benefits in controlling anxiety, psychosis, inflammation, epilepsy and demonstrated neuroprotective effects.

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, according to data from the National Cancer Institute (INCA). 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. 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.
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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...
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. 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.

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 PRISMA 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 |

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

<table>
<thead>
<tr>
<th>Title</th>
<th>Author/Country</th>
<th>Year</th>
<th>Goal</th>
<th>Method</th>
<th>Result</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>Amato L et al, 2017 / Italia</td>
<td></td>
<td>Provide evidence of the benefits and harms of cannabis treatment.</td>
<td>Systematic Review</td>
<td>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,</td>
<td>Moderate</td>
</tr>
<tr>
<td>Provider perspectives on use of medical marijuana in children with cancer</td>
<td>Ananth P et al., 2017 / USA</td>
<td></td>
<td>Investigate physician perspectives on the legal use of MM in children with cancer.</td>
<td>Quantitative cross-sectional study</td>
<td>Most pediatric oncology providers are willing to consider the use of MM in children with cancer and receive frequent inquiries</td>
<td>Low</td>
</tr>
<tr>
<td>Oral medicinal cannabinoids to relieve symptom burden in the palliative care of patients with advanced cancer</td>
<td>Good P et al., 2019 / USA</td>
<td></td>
<td>This study aims to define the role of cannabidiol (CBD) in symptom burden management in patients with advanced cancer in standard palliative care</td>
<td>Randomized Clinical Trial</td>
<td>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</td>
<td>Low</td>
</tr>
</tbody>
</table>
### Tabela 1 – Cont.

<table>
<thead>
<tr>
<th>Topic</th>
<th>Study</th>
<th>Methodology</th>
<th>Conclusion</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living with a hope of survival is challenged by a lack of clinical</td>
<td>Buchwald et al., 2019 / USA</td>
<td>Qualitative observational study</td>
<td>Most patients reported relief of symptoms, such as insomnia, anxiety, nausea, and pain, after starting treatment with CBM, but this outcome was</td>
<td>Very low</td>
</tr>
<tr>
<td>evidence:</td>
<td></td>
<td></td>
<td>perceived as less of a focus compared to hope for cure.</td>
<td></td>
</tr>
<tr>
<td>Cannabis surveillance with twitter data: emerging topics and social</td>
<td>Allem; Escobedo; Dharmapuri, 2020 / USA</td>
<td>Qualitative observational study</td>
<td>The predominant topics of posts included cannabis use with mentions of cannabis initiation, processed cannabis products, and health and medical</td>
<td>Low</td>
</tr>
<tr>
<td>bots</td>
<td></td>
<td></td>
<td>with posts suggesting that cannabis can help with cancer, sleep, pain, anxiety, depression, trauma, and post-traumatic stress disorder.</td>
<td></td>
</tr>
<tr>
<td>Cannabinoids for adult cancer-related pain</td>
<td>Boland EG et al., 2019 / England</td>
<td>Systematic review and meta-analysis</td>
<td>There was no difference between cannabinoids and placebo for the difference in the change in mean pain scores on the High Numeric Rating Scale.</td>
<td></td>
</tr>
<tr>
<td>The efficacy of medical marijuana in the treatment of cancer-related</td>
<td>Ian M et al., 2019 / USA</td>
<td>Cohort study</td>
<td>ESAS scores for pain, physical, emotional and total scores improved in severe MMJ (-) and MMJ (+); opioid consumption was reduced by 22% in MMJ</td>
<td>Moderate</td>
</tr>
<tr>
<td>pain</td>
<td></td>
<td></td>
<td>(-) (135-106 mg / day MME, p = 0.124) and 33% in MMJ (+) (90-60 mg / day MME, p = 0.421)</td>
<td></td>
</tr>
<tr>
<td>Therapeutic use of cannabis and cannabinoids: an evidence mapping</td>
<td>Montero-Oleas et al., 2020 / Spain</td>
<td>Systematic review</td>
<td>The evidence on the medical use of cannabis is ample. However, due to methodological limitations, conclusions were weak in most of the comparisons</td>
<td>Moderate</td>
</tr>
<tr>
<td>and appraisal</td>
<td></td>
<td></td>
<td>evaluated.</td>
<td></td>
</tr>
<tr>
<td>Cannabis: A Toxin-producing Plant with potential Therapeutic uses</td>
<td>Breijyeh et al., 2021 / Israel</td>
<td>Systematic review</td>
<td>Between the promising therapeutic advantages, high abuse tendency and safety concerns, additional research efforts are still needed to better</td>
<td>Low</td>
</tr>
<tr>
<td>Opioid-sparing effects of medical cannabis or cannabinoids for chronic</td>
<td>Noori A et al., 2020 / Canada</td>
<td>Systematic review</td>
<td>understand the interactions of cannabinoids within the human body and to explore the potential medical applications of cannabis</td>
<td>Very low</td>
</tr>
<tr>
<td>pain</td>
<td></td>
<td></td>
<td>Opioid dose reduction, pain relief, sleep disturbance, physical and emotional functioning, and adverse events.</td>
<td></td>
</tr>
</tbody>
</table>
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 scientists with potential therapeutic target in numerous pathological conditions. 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.\textsuperscript{17,19} It was reported in the study by Amato L et al\textsuperscript{20} 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.\textsuperscript{17,20} This evidence is in line with the study by Ananth P et al,\textsuperscript{21} which highlights the alterations in the endocannabinoid system associating them with growth, migration, and the invasion of some tumors.\textsuperscript{21} Cannabinoids have been tested in several types of cancer, including brain, breast, and prostate cancer.\textsuperscript{6,17,18} The study by Braun et al\textsuperscript{22} reports that cannabinoids have shown promise as analgesics for the treatment of inflammatory and neuropathic pain.\textsuperscript{2,5} In research by Good P et al\textsuperscript{24} 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.\textsuperscript{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.\textsuperscript{23} Most studies on cannabis use patterns among cancer patients are limited to a single site lacking large-scale studies.\textsuperscript{23} This result corroborates with the work of Noori A et al,\textsuperscript{26} which showed that Colombian psychiatrists have a favorable attitude toward prescribing medical cannabis; however, there is a serious lack of legal knowledge.\textsuperscript{23-26}

An interesting finding in the study by Kaufmann et al,\textsuperscript{8} was that most physicians agreed with the use of (CM) to combat chronic cancer-related pain receiving the highest approval with 87.6\textsuperscript{%.24,25,26} The systematic review by Montero-Oleas\textsuperscript{28} 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).\textsuperscript{25} The systematic review by Amato et al\textsuperscript{20} 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.\textsuperscript{26} The study by Silva et al\textsuperscript{5} 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).\textsuperscript{24} No treatment-related deaths were reported. The dropout and mortality rates were high.\textsuperscript{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**


Therapeutic benefits of cannabinoids in the treatment of chronic pain in cancer patients


