Use of cannabis and its derivates in chronic pain management: systematic review

Uso de cannabis e seus derivados no manejo da dor crônica: revisão sistemática

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ABSTRACT

BACKGROUND AND OBJECTIVES: Chronic pain is a clinical condition that affects an important part of the Brazilian and world population, significantly affecting their lives. The medicinal properties of Cannabis have been explored for millennia, but recently its use for the relief of chronic pain symptoms has increased.

CONTENTS: A systematic review was carried out with the objective of evaluating the use of cannabis and its derivatives in the management of chronic pain, analyzing its potential side effects and safety. For this, the following databases were used: Pubmed, Embase, Cochrane Library and BVS, searching for studies published in the last 5 years, in Portuguese, Spanish or English, using MeSH descriptors and relevant free terms. Randomized, double-blind clinical trials with at least 10 participants in each comparison arm and with at least 2 weeks of intervention were included. After screening the authors, a quantitative analysis of 4 clinical trials (586 patients) was performed, which were analyzed for the outcomes of: patients with 50% or 30% reduction in pain intensity compared to baseline, improvement in pain intensity average pain, discontinuation due to adverse effects, serious adverse effects, and any adverse effects.

CONCLUSION: The analysis did not yield high-quality evidence pertaining to the evaluation of efficacy, safety, or adverse effects associated with the use of cannabis-derived treatments in the management of chronic pain. Consequently, the formulation of recommendations or restrictions in these regards is not feasible, leaving the utilization of these therapeutic modalities subject to individual assessment.

Keywords: Cannabidiol, Cannabis, Chronic pain, Dronabinol, Systematic review.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A dor crônica é uma condição clínica que atinge parte importante da população brasileira e mundial, afetando significativamente a vida dessas pessoas. As propriedades medicinais da Cannabis vêm sendo exploradas por milênios, mas recentemente seu uso para alívio dos sintomas da dor crônica tem aumentado.

CONTEÚDO: Foi conduzida uma revisão sistemática com o objetivo de avaliar o uso de cannabis e seus derivados no manejo da dor crônica, analisando seus potenciais efeitos adversos e sua segurança. Para isso, foram utilizadas as seguintes bases de dados: Pubmed, Embase, Cochrane Library e BVS, buscando estudos publicados nos últimos 5 anos, nos idiomas português, espanhol ou inglês, utilizando os descritores MeSH e termos livres relevantes. Foram incluídos ensaios clínicos randomizados, duplos-cegos, com pelo menos 10 participantes em cada braço de comparação e com no mínimo 2 semanas de intervenção. Após a triagem dos autores, foi procedida a análise quantitativa de 4 ensaios clínicos (586 pacientes), que foram analisados para os desfechos de: pacientes com redução da intensidade da dor 50% ou 30% em relação à linha de base, melhora na intensidade média da dor, descontinuidade devido a efeitos adversos, efeitos adversos graves e qualquer efeito adverso.

CONCLUSÃO: Não foram encontradas evidências de alta qualidade quanto à avaliação dos desfechos de eficácia, segurança ou de efeitos adversos relacionados ao uso de tratamentos derivados da cannabis no manejo de dor crônica, não podendo ser produzidas recomendações ou restrições nesses aspectos, ficando o uso dessas modalidades terapêuticas sujeito a análise individual.

Descritores: Canabidiol, Cannabis, Dor crônica, Dronabinol, Revisão sistemática

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HIGHLIGHTS

- The traditional treatment of chronic pain consists of the use of analgesic drugs and physiotherapeutic treatment modalities with a variable response and short-lived improvement results.
- The variety of pain measurement scales, even greater in this review due to the variety of conditions included, makes it difficult to generalize the use of cannabis-derived treatments for the treatment of chronic pain in these conditions.
- The use of cannabis-derived treatments for chronic pain requires a careful assessment of each individual situation.

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INTRODUCTION

Pain is a symptom that can last for a long time, with a period of three months being a benchmark for defining chronic pain (CP). In these situations, pain becomes a problem in itself, and various conditions can lead to CP, such as nerve damage, autoimmune diseases and osteomyoarticular diseases[1]. The impact of CP on the health of the world's population and the increase in its prevalence in recent years awakened the need for therapeutic approaches to its treatment[2]. Data on the prevalence of CP in adults ranges from 20% in the United States to almost 40% in Brazil[3,4].

The definition of pain as ''an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage", thus encompassing both sensory and emotional aspects[1], justifies a multidisciplinary approach to treating this condition[5-7]. In addition, CP is associated with impaired sleep quality, ability to carry out daily activities, work performance, social life and mental health, including the association with psychological disorders such as anxiety[6,8,9].

The traditional treatment of CP consists of the use of analgesic drugs and physiotherapeutic treatment modalities with a variable response and short-lived improvement results[1]. A high cost is associated with frequent visits by people with CP, seeking medical attention, complementary exams, physiotherapist and psychologist appointments, as well as the cost of drugs. Added to the indirect costs of the low productivity of people with CP, this places a high burden on society[10-12]. In addition to the variable results in response to conventional treatment with partial pain relief[13], the prolonged use of drugs, such as opioids, is associated with unwanted adverse effects and the possibility of addiction[14], so approach strategies with better tolerability and better quality of evidence are being sought in clinical trials[15,16].

Among the new pharmacological options, randomized clinical trials have investigated the action of two of the most studied cannabinoids with the greatest therapeutic properties, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)[17,18]. THC is a compound with analgesic and anti-inflammatory properties[19], which makes it a frequent subject of research into the treatment of conditions such as CP, controlling nausea and vomiting in chemotherapy patients, and increasing appetite in patients with anorexia[18]. Dronabinol corresponds to the synthetic form of THC, which has been approved for use in several countries, such as the United States, Canada, Germany and the United Kingdom (BfArM, FDA, Health Canada, NICE). The FDA has approved it since 1985, and the drug is currently approved for the treatment of nausea and vomiting and loss of appetite in special situations, as well as being used off-label for the treatment of CP[20]. CBD, unlike THC, has no psychoactive properties and does not yet have a fully understood mechanism of action, but it does have anti-inflammatory and analgesic effects and may have less potential for adverse effects than THC[21]. Studies have focused on its therapeutic use for treating epilepsy, anxiety, CP, sleep disorders and controlling chronic inflammatory diseases[18].

Given the different interactions of cannabinoids with the mechanisms involved in pain modulation[19,22,23], their therapeutic potential in patients with CP has been investigated[17,18], encompassing their various presentations, dosages, routes of administration and etiologies of CP[18,24].

Thus, the aim of this study was to elucidate available evidence from randomized clinical trials on the use of cannabis and its derivatives in the treatment of CP available in scientific article databases, seeking to identify its efficacy and safety profile and adverse effects arising from this intervention, through qualitative analysis and using statistical measures to assess the effect promoted by the potential therapeutic measure.

CONTENTS

This is a systematic review study that followed the recommendations of the PRISMA protocol (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[25].

Foi realizada estratégia de busca detalhada, utilizando os descritores MeSH X e Y e termos livres relevantes associados a operadores booleanos 'OR' e 'AND'. A estratégia de busca foi aplicada nas seguintes bases de dados: PubMed, Embase, Cochrane Library e BVS, publicados nos últimos 5 anos, nos idiomas português, espanhol e inglês, conforme apresentado nas tabelas de 1 a 4.

Table 1. Search strategy

Virtual Health Library
1. Chronic Pain (Descriptors in Health Sciences - DeCS)
2. AND
3. Cannabis
a. OR
b. Cannabidiol
c. OR
d. Dronabinol
e. OR
f. Tetrahydrocannabinol
4. Filter: Full text: Available
5. Filter: Type of study: Randomized clinical trial
6. Filter: Languages: English, Spanish, Portuguese
7. Filter: Full text available
8. Filter: Publication year range: 2018 to 2023
EMBASE
In the advanced search tab, using Emtree terms (Embase Subject Headings)
#1 Chronic pain'/exp
#2 Cannabis'/exp OR cannabidiol/exp OR dronabinol/exp OR tetrahydrocannabinol/exp
#3 #1 AND #2
#4 #1 AND #2 AND [randomized controlled trial]/lim AND ([english]/lim OR [portuguese]/lim OR [spanish]/lim) AND [2018-2023]/py
Pubmed
Using MeSH terms (Medical Subject Headings)
1. (Chronic pain)
2. AND
3. ((((cannabis) OR (cannabidiol)) OR (dronabinol)) OR (tetrahydrocannabinol))
4. Filter: Full text
5. Filter: Randomized Controlled Trial
6. Filter: English, Portuguese, Spanish
7. Filter: Humans
8. Filter: in the last 5 years

Continue...

Table 1. Search strategy – continuation

COCHRANE
In the advanced search tab, using MeSH terms (Medical Subject Headings)
#1 [Chronic Pain]/explode all trees]
#2 [Cannabis]/exp
#3 (Cannabidiol or dronabinol or tetrahydrocannabinol):ti, ab, kw
#4 #2 OR #3
#5 #1 AND #4
#6 Filter: "Trials"
#7 Filter: Custom year range 2018-2023

Study selection

Two independent reviewers (BM and DN) carried out the initial screening of titles and abstracts, based on the predefined inclusion criteria: randomized, double-blind clinical trials evaluating the use of cannabis in the treatment of CP in humans, with published full text. The exclusion criteria were: trials with fewer than 10 participants in each comparison arm, efficacy of the intervention not included in the primary endpoint, intervention for less than two weeks and the need for an imputation method to analyze the result.

The selected studies were subjected to a full analysis by the same two reviewers, who assessed eligibility according to the inclusion and exclusion criteria, resolving differences by consensus (Figure 1).

Risk of bias assessment

The Cochrane Risk of Bias (RoB) instrument was used to assess the risk of bias of the included studies. The same two independent reviewers (BM and DN) assessed the risk of bias for each study, using the RoB, and classified the studies as low risk, uncertain risk or high risk of bias in each assessment domain, resolving the differences by consensus (Figure 2), classifying the studies as: high quality - from zero to two uncertain risks of bias; moderate quality - from three to five uncertain risks of bias; and low quality - from six to eight uncertain risks of bias, or at least a high risk of bias[26].

Quality of evidence assessment

The quality of the evidence was assessed using the GRADE methodology (Grading of Recommendations, Assessment, Development and Evaluation). The same two independent reviewers (BM and DN) assessed the quality of the evidence for each outcome considered important for decision-making, evaluating the domains of risk of bias, inconsistency, imprecision, publication bias and other factors that could affect confidence in the estimates of effect.

The classification was carried out using the GRADE software, on the GRADEpro® platform, with an automated result after filling in the topics, in terms of the quality of evidence: high quality, moderate quality, low quality and very low quality (Table 2).

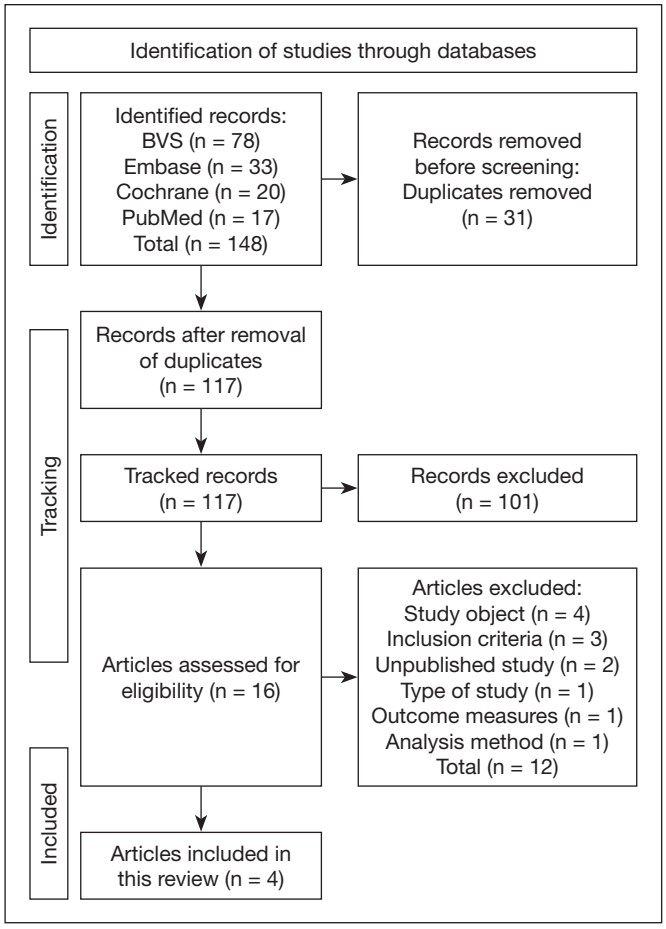

Figure 1. Study selection

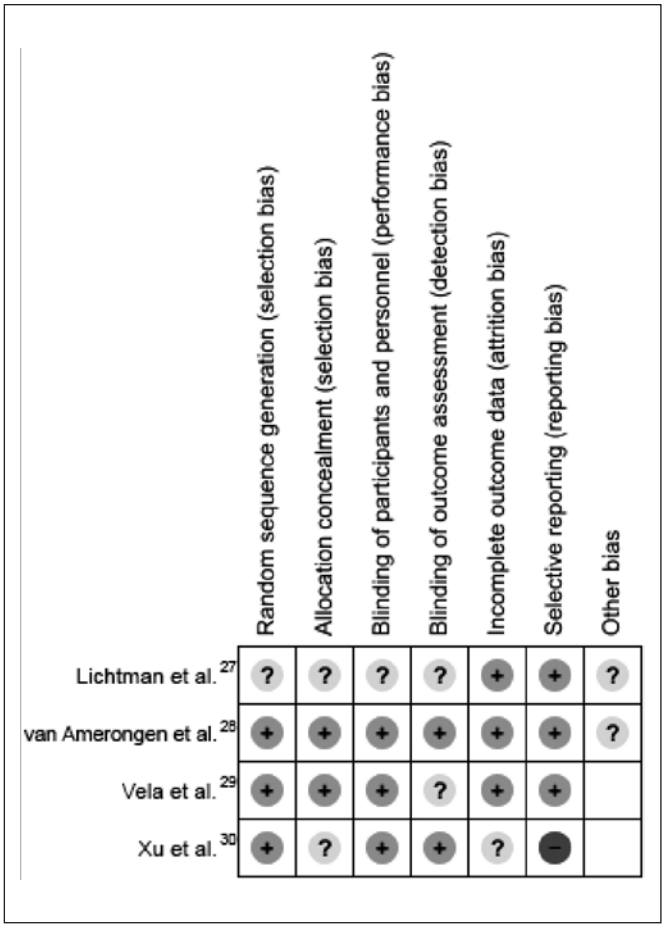

Figure 2. Risk of bias summary

Table 2. Assessing the Certainty of Evidence – GRADE

Evaluation of certainty							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	[Cannabis]	[placebo]	Relative (95% CI)	Absolute (95% CI)		
Patients with 50% improvement in pain												
2	RCT	Not severe	Not severe	Very severe[a]	Very severe[b]	None	32/269 (11.9%)	30/264 (11.4%)	**OR 1.04** (0.60 to 1.79)	**4 more per 1,000** (from 42 less to 73 more)	⊕◯◯◯ Very low	Critical
Patients with 30% improvement in pain												
2	RCT	Not severe	Not severe	Very severe[a]	Very severe[b]	Highly suspicious publication bias[c]	80/269 (29.7%)	71/264 (26.9%)	**OR 1.15** (0.78 to 1.68)	**28 more per 1,000** (from 46 less to 113 more)	⊕◯◯◯ Very low	Important
Average improvement on the pain scale												
4	RCT	Not severe	Not severe	Severe[d]	Very severe[b]	Highly suspicious publication bias[c]	296	290	-	**SMD 0.14 SD higher** (0.03 less to 0.3 more)	⊕◯◯◯ Very low	Important
Discontinuation due to adverse effects												
4	RCT	Not severe	Not severe	Severe[d]	Very severe[b]	Highly suspicious publication bias[c]	40/296 (13.5%)	38/290 (13.1%)	**OR 1.08** (0.66 to 1.77)	**9 more per 1,000** (from 41 less to 80 more)	⊕◯◯◯ Very low	Critical
Severe adverse effects												
4	RCT	Not severe	Not severe	Severe[d]	Very severe[b]	Highly suspicious publication bias[c]	49/296 (16.6%)	45/290 (15.5%)	**OR 1.10** (0.70 to 1.75)	**13 more per 1,000** (from 41 less to 88 more)	⊕◯◯◯ Very low	Critical
Any adverse effects												
4	RCT	Not severe	Not severe	Severe[d]	Very severe[b]	Highly suspicious publication bias[c]	212/296 (71.6%)	198/290 (68.3%)	**OR 1.09** (0.40 to 2.96)	**18 more per 1,000** (from 220 less to 182 more)	⊕◯◯◯ Very low	Important

RCT = randomized clinical trial; a. Two different populations, one of the articles[21] deals with cancer patients and the other[29] deals with patients with psoriasis or hand OA.
b. CI crosses the center line.
c. More than 70% of the data entered comes from studies funded by the pharmaceutical industry.
d. There is a wide variety of groups, but different drugs, dosages and even routes of drug administration are used.

Data extraction and synthesis

The relevant data from the included studies was extracted independently by the same two reviewers (BM and DN), including information on the study design, intervention, outcomes, results and information relevant to assessing the risk of bias and the quality of the evidence, with disagreements being resolved through discussion. The data was synthesized considering the heterogeneity between the studies.

For dichotomous data, the random effect model was used to calculate the Odds Ratio (OR), with a 95% confidence interval (CI), calculating the number needed to treat (NNT) in the efficacy outcomes as the inverse of the absolute risk reduction and the cut-off value as 10 for a clinically relevant beneficial outcome[38]. For continuous data, the random effect model was used to calculate the Standardized Mean Differences (SMD). When the standard deviation (SD) was not available, it was calculated using t-value, p-value, CI or standard error (SE).

No imputation method was used for the data from the included studies. For the data analysis method, intention-to-treat (ITT) analysis was used for patients who were randomized and took at least one dose of the drug.

As for data derived from crossover trials, preference was given, when available, to data referring to the period prior to the crossover, avoiding the biases inherent in this type of study.

Given this unavailability, in order to allow comparisons to be made, the data was analyzed at the end of the study, since the washout period was reported to avoid the carry-over effect, as guided by the Cochrane Handbook for Systematic Reviews of Interventions.

Outcome measures

Due to the variety of methods for evaluating interventions in the management of CP, possible outcome markers were predicted. Thus, the outcomes of the articles were evaluated according to the recommendations for evidence in CP[31-33], using the definitions of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) for substantial (primary) and moderate (secondary) outcomes.

As for those defined as primary outcomes: reduction in pain intensity by at least 50% compared to baseline, achieving pain intensity of less than 30% on the pain scale and intensity no worse than mild pain. However, the other markers were assessed as presented, such as a reduction in pain intensity of at least 30% compared to baseline, improvement in average pain intensity, a much better or markedly better overall impression of the patient, achieving pain intensity of less than 50% on the pain scale, functional assessment or quality of life measure.

Evaluation of heterogeneity

Heterogeneity between studies was assessed visually through forest plots and using p-value and the I^2 statistic, which measures the proportion of variability between studies due to heterogeneity rather than chance, using $p > 0.05$ for no statistically significant heterogeneity and $I^2 > 50\%$ as significant heterogeneity.

Sensitivity and subgroup analyses were not possible due to the small number of studies (4). The analyses were carried out using Review Manager 5® software (RevMan 5). The results were presented in tables and/or figures and interpreted considering the quality of the evidence and the heterogeneity found.

RESULTS

The results of this research are detailed in a PRISMA diagram[34]. The electronic search reached 148 publications. Removing duplicate files using Mendeley® software (automatically and manually) resulted in 117 publications, 101 of which were excluded after reading the titles and abstracts. Twelve studies were excluded after reading all the studies, for reasons illustrated in the PRISMA diagram. The remaining four studies were included in this review.

Included studies

This review included two randomized clinical trials[27,29] and two crossover clinical trials[28,30]. The studies included were published between 2018 and 2021. A more detailed analysis of the studies can be found in tables 2 and 3.

One study had very short duration (two to four weeks)[28]; the other three studies had short duration (four to 12 weeks)[27,29,30].

One of the studies was multicenter[27], carried out in Belgium, Bulgaria, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, the United Kingdom and the United States. The other three studies were single-center: Denmark[29], the United States[30] and the Netherlands[28].

Sample sizes ranged from 24 to 399 participants[27,30].

Two studies were funded by the pharmaceutical industry[27,28], the others came from foundations interested in the research[29] or without external funders, just donations of the product[30].

The study included adult patients aged 18 and over with CP, including neuropathic pain, from a wide variety of sources: cancer, fibromyalgia and other forms.

Two of the studies reported no previous contact with any form of cannabis[27,28], one of the studies reported patients' previous contact with recreational cannabis[30] and one put dependence/abuse as an exclusion factor, but was not clear about recreational use[29].

With regard to the types of cannabis-derived drugs used, three of the studies used oral forms of administration, one of them in the form of a TCH/CBD oromucosal spray (Nabiximols)[27], one in the form of oral THC[28] and another of oral CBD[29]. One study used the topical form of CBD administration[30]. All the studies[27-30] compared its effects with placebo.

Three of the studies reported no impediment to the use of rescue therapies for acute pain relief during the periods analyzed[28-30]. One of the studies allowed only one type of rescue drug, with the exclusion criterion being use above this limit[27].

As for the possibility of concomitant therapy, none of the studies reported any impediment to the concomitant use of basic therapies[27-30], except for the concomitant or previous use - in the last three months - of corticosteroids[29] and a change in the spasmolytic dose during the study or thirty days before[28].

Risk of bias in included studies

The risk of bias in most domains was low in all studies (Figure 2). The overall quality risk of the studies was defined according to the Cochrane risk of bias criteria, with two studies being of high quality[28,29], one of moderate quality[27] and one of low quality[30]. The low-quality study, i.e. with a high risk of bias, had less than 5% participation in the total sample, so there was no need to exclude it from the study (Table 3).

Effects of interventions: primary outcome

A total of 533 participants were analyzed. Thirty-two (11.9%) of the participants who underwent the cannabis-derived treatments and 30 (11.4%) of the participants in the placebo group reported a 50% or greater improvement in pain [(Odds Ratio - OR 1.04, 95% CI 0.60 to 1.79); p-value 0.89; I^2 = 0%]. NNT was 200 for the pooled intervention group. According to what was pre-established, there is no relevant clinical benefit in cannabis-derived treatments (Figure 3). The quality of evidence was very low, downgraded due to indirect evidence (variability of groups, interventions) and imprecision (CI includes zero).

A total of 586 participants were analyzed. Forty (13.5%) of the participants who underwent cannabis-derived treatments and thirty-eight (13.1%) of the participants in the placebo group reported at least one adverse effect [(OR 1.08, 95% CI 0.66 to 1.77); p-value 0.75; I^2 = 0% (Figure 4)].

A total of 586 participants were analyzed. Forty-nine (16.5%) of the participants who underwent cannabis-derived treatments and 145 (15.5%) of the participants in the placebo group reported a serious adverse effect [(OR 1.10, 95% CI 0.70 to 1.75); p-value 0.67; I^2 = 0% (Figure 5)].

Table 3. Included studies

Authors	Type of Study	Population	Groups	Intervention	Outcomes	Notes
Lichtman et al.[27]	RCT double-blind	Cancer patients with uncontrolled chronic pain.	Control group: Age 60.7; Gender (H): 52%; Ethnicity (White) 93.4%; Time since cancer diagnosis 3.3 years; Mean NRS 5.6; Time since onset of pain 1.7 years. Intervention group: Age 59.2; Gender (H): 55.8%; Ethnicity (White) 93% Time since cancer diagnosis 3.3 years; mean NRS 5.6; Time since onset of pain 1.7 years.	Nabiximols (spray - oral mucosa) (THC: 27mg/dL CBD: 25mg/dL) vs Placebo. Duration: 2 weeks of dose titration + 3 weeks of intervention.	Patients with 50% improvement in pain, patients with 30% improvement in pain, improvement in average pain intensity. Discontinuation due to adverse effects, serious adverse effects and patients with adverse effects.	-
van Amerongen et al.[28]	RCT Crossover	Patients with progressive multiple sclerosis.	Control group: Age 51.4 years; Gender (H): 33.3%; Time of illness: 12.6 years. Intervention group: Age 57.3 years; Gender (H): 33.3%; Time of illness: 10.3 years.	THC (Oral) 9-29mg/d vs Placebo. Duration: 4 weeks.	Improvement in average pain intensity. Discontinuation due to adverse effects, serious adverse effects and patients with adverse effects.	Form of recruitment not specified
Vela et al.[29]	RCT double-blind	Patients with psoriasis or osteoarthritis of the hands.	Control group: Age 61.5; Gender (H): 30%; Average VAS 6.1; Distribution: Psoriatic arthritis 42% (28), Hand osteoarthritis 58% (38). Intervention group: Age 62; Gender (H): 40%; Mean VAS 5.2; Distribution: Psoriatic arthritis 44% (31), Hand osteoarthritis 56% (39).	CBD (oral) 20-30mg/d vs Placebo. Duration: 12 weeks.	Patients with 50% improvement in pain, patients with 30% improvement in pain, improvement in average pain intensity. Discontinuation due to adverse effects, serious adverse effects and patients with adverse effects.	It doesn't mention the recruitment method.
Xu et al.[30]	RCT Crossover	Patients with peripheral neuropathy in the lower limbs.	Control group: Age 66.6 years; Gender (H): 50%; Previous use of CBD (n): 5 participants: Etiology of neuropathic pain (n): 9 diabetes mellitus, 2 pharmacological, 2 idiopathic, 1 embolism. Intervention group: Age 69.5 years; Gender (H): 73.3%; Previous use of CBD (n): 2 participants: Etiology of neuropathic pain (n): 9 diabetes mellitus, 1 pharmacological 1 idiopathic, 1 sciatica.	CBD Oil (Topical) (250 mg CBD/3 fl. oz) vs Placebo. Duration: double-blind 4 weeks + open study 4 weeks.	Improvement in average pain intensity. Discontinuation due to adverse effects, serious adverse effects and patients with adverse effects.	Data used only from the first 4 weeks (double-blind), excluding data from the open study phase.

RCT = randomized clinical trial.

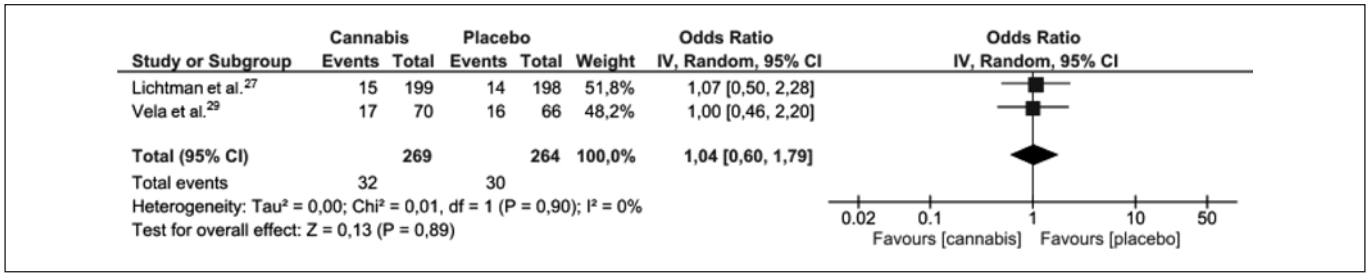

Figure 3. Forest-plot: patients with 50% improvement in pain

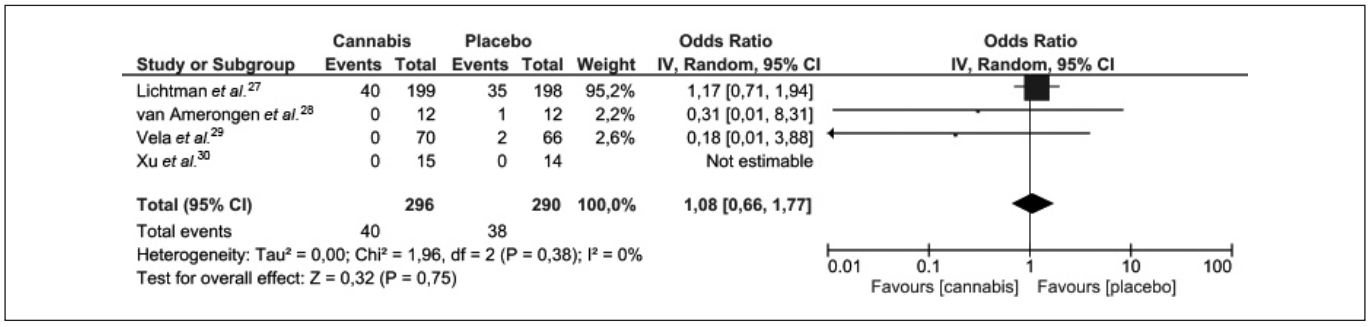

Figure 4. Forest-plot: study discontinued due to adverse effects

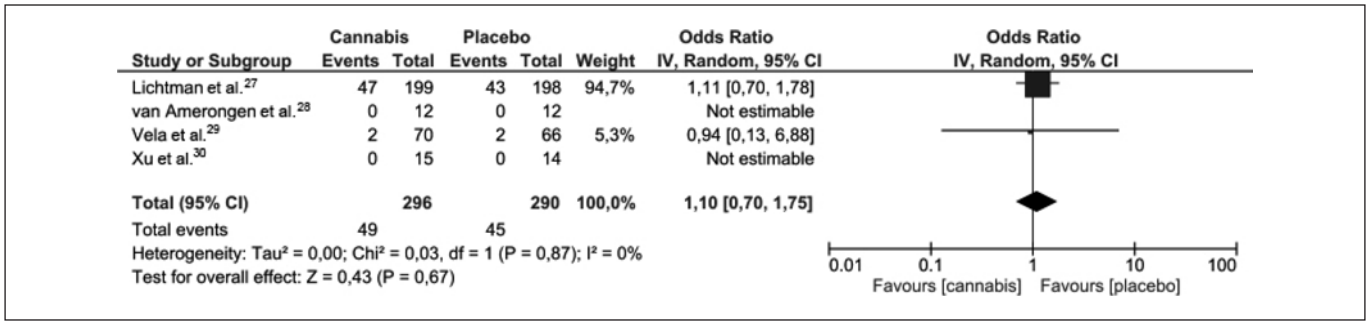

Figure 5. Forest-plot: serious adverse effects

The primary outcomes of achieving pain intensity of less than 30% on the pain scale and pain intensity no worse than mild pain were not reported in the included studies.

Effects of interventions: secondary outcome

A total of 533 participants were analyzed. Eighty (29.7%) of the participants who underwent the cannabis-derived treatments and seventy-one (26.9%) of the participants in the placebo group reported an improvement of 30% or more in pain [(OR 1.15, 95% CI 0.78 to 1.68); p-value 0.89; I^2 = 0%]. NNT was 36 for the pooled intervention group (Figure 6). According to what was pre-established, there was no relevant clinical benefit in cannabis-derived treatments (Figure 3). The quality of evidence was very low, downgraded due to indirect evidence (variability of groups, interventions), imprecision (CI includes zero) and publication bias (more than 70% of the data came from studies funded by the pharmaceutical industry).

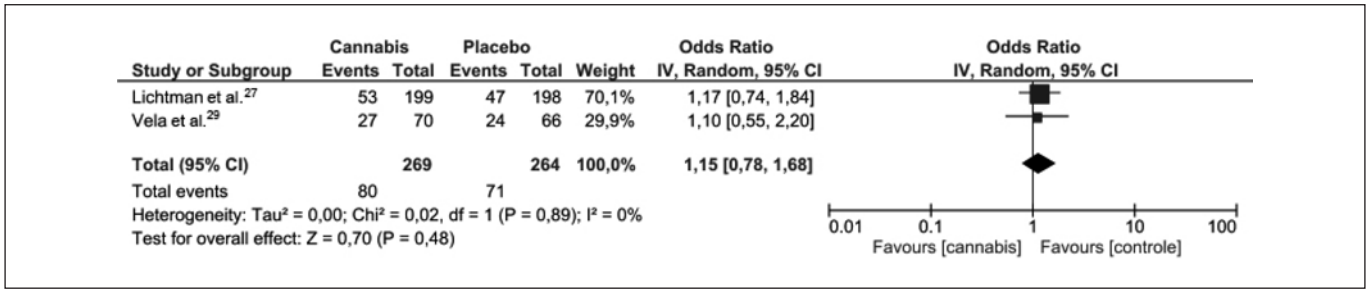

Figure 6. Forest-plot: patients with 30% improvement in pain

A total of 586 participants were analyzed. Cannabis-derived treatments were superior to placebo in reducing mean pain intensity (Standardized Mean Difference - SMD - 0.14, 95% CI 0.30 to 0.03; p-value 0.10. $I^2 = 0\%$). According to what was pre-established, there was no relevant clinical benefit in cannabis-derived treatments (Figure 7). The quality of evidence was very low, downgraded due to indirect evidence (variability of groups, interventions), imprecision (CI includes zero) and publication bias (more than 70% of the data came from studies funded by the pharmaceutical industry).

A total of 586 participants were analyzed. Two hundred and twelve (71.6%) of the participants who underwent cannabis-derived treatments and 198 (68.3%) of the participants in the placebo group reported at least one adverse effect [(OR 1.09, 95% CI 0.40 to 2.96); p-value 0.87; $I^2 = 64\%$ (Figure 8)].

Secondary outcomes were not reported: patient's overall impression much better or markedly better, achieving pain intensity of less than 50% on the pain scale, functional assessment, or quality of life measure.

Subgroup analysis and sensitivity analysis

Subgroup analysis was not carried out due to the number of studies being less than 10, which compromises the analysis, leading to disproportions when defined by subgroups.

Sensitivity analysis was not carried out because the weight of the group with a high risk of bias[30] was less than 5%, ruling out the need for this analysis.

Heterogeneity

I^2 was lower than 50% for patients with 50% or more improvement in pain, discontinuations due to adverse effects, serious adverse effects, patients with 30% or more improvement in pain, and improvement in mean pain intensity. However, I^2 was higher than 50% for patients with any adverse event ($I^2 = 64\%$). No clinical explanations were found for the heterogeneity.

Excluded studies

Twelve studies were excluded for the following reasons: three studies were excluded for having objects other than the efficacy of the use of cannabis in the treatment of CP[34-37]; two for not meeting the inclusion criteria regarding the minimum intervention time of two weeks[38,39]; two for not having published results[40,41]; one for not being double-blind randomized[42]; one because it did not meet the inclusion criteria in terms of the minimum number of 10 participants in each arm of the study[43]; one because it did not present outcome measures for pain despite being included in the methodology outcomes[44]; one because it presented a data analysis method other than intention to treat[45]. The reasons for excluding the studies are summarized in table 4.

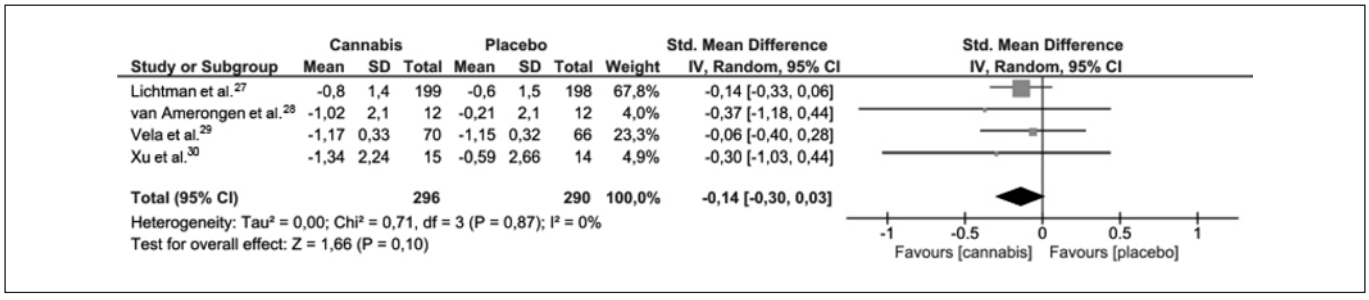

Figure 7. Forest-plot: improvement in average pain intensity

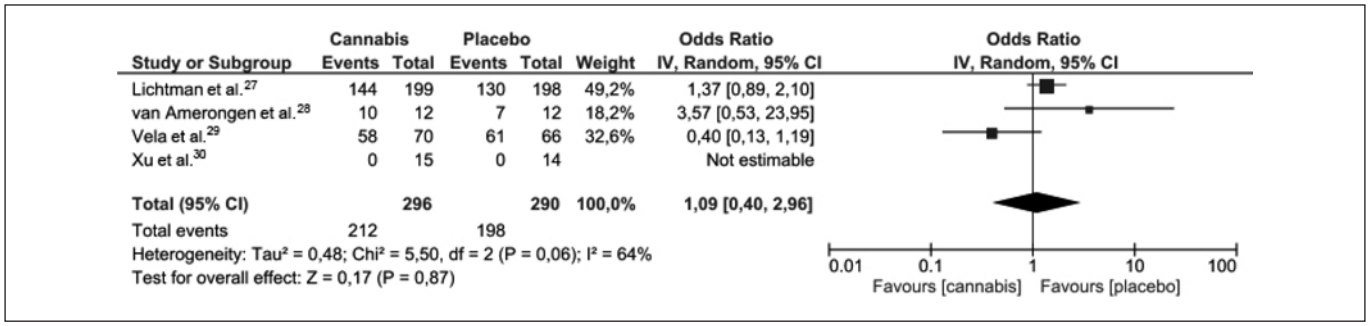

Figure 8. Forest-plot: patients affected by adverse effects

Table 4. Excluded studies

Studies	Reason for exclusion
Abrams et al.[45]	The method of data analysis was not by intention to treat.
Alessandria et al.[34]	Object of the different study of the efficacy of cannabis-derived treatments for chronic pain.
Almog et al.[35]	Object of the different study of the efficacy of cannabis-derived treatments for chronic pain.

Comtinue...

Table 4. Excluded studies – continuation

Studies	Reason for exclusion
Almog et al.[38]	Intervention time less than two weeks.
Chaves, Bittencourt and Pelegrini[43]	Number of participants per treatment group less than 10 participants.
Gao et al.[44]	It has no outcome measures for pain in the treatment phase.
NCT03984565[40]	Results not yet published.
Poli et al.[42]	It is not a randomized double-blind clinical trial.
Sharon et al. [36]	Object of the different study of the efficacy of cannabis-derived treatments for chronic pain.
Van Dam et al.[41]	Results not yet published.
Van de Donk et al.[39]	Intervention time less than two weeks.
Weizman et al.[37]	Object of the different study of the efficacy of cannabis-derived treatments for chronic pain.

DISCUSSION

Four studies were included, lasting between four and 12 weeks, with 586 participants. All the studies compared cannabis-derived treatments with placebo. The studies compared oromucosal spray with a combination of THC and CBD, oral THC, oral CBD and topical CBD oil, with one study for each combination. There was no difference between any type of cannabis-derived treatment and placebo in the number of patients with substantial improvement (50% or more) in pain (very low quality of evidence), in the number of patients with moderate improvement (30% or more) in pain (very low quality of evidence) or in the reduction in average pain intensity (very low quality of evidence).

There was no difference in the cannabis-derived treatments put together in terms of the frequency of serious adverse effects, withdrawal from the study due to adverse effects or any adverse effects. There was no high-quality evidence for any of the cannabis-derived treatments having value in treating patients with CP. Several factors limited the applicability of the evidence in this review: baseline levels of CP parameters varied between studies, use of different measurement scales, different forms of pain manifestation, heterogeneity of conditions and populations, and variable sample values for each type of condition, not necessarily reflecting the general population with CP.

In addition, the variety of ways of dealing with patients with a history of late or recent previous cannabis use in the included studies, exclusion in the case of a history of dependence, and the lack of knowledge of the possibility of a difference in therapeutic or adverse effects in patients with previous use. What's more, the limitations inherent in the methodological design adopted in this study, such as the time frame of publications in the last five years and the languages analyzed, compromised the robustness of the evidence, as it disregarded trials that could alter the result of the statistical analysis.

The different approaches to allowing concomitant therapies, the use of rescue drugs as limiting factors in the evidence, the length of the studies and the follow-up times, the longest of which was 12 weeks, made it impossible to assess the long-term outcome. The applicability of the evidence to routine clinical care was limited due to the exclusion of patients with a history of substance abuse, psychiatric illnesses and pregnant women.

The quality of evidence for all outcomes was very low due to indirect evidence and imprecision (all measured outcomes crossed the confidence interval). Thus, the estimates of effects presented in this study are susceptible to important changes in the event of the publication of additional research with a higher quality of evidence. Some outcomes showed publication bias, due to the large presence of data from studies funded by the pharmaceutical industry.

Two of the studies included in this review used a crossover design with reduced duration and sample sizes, one of them with data only from the first phase[30], in an attempt to reduce the methodological effects of this type of study[46], and the other reporting an accrual period. These effects can interfere with the results of a meta-analysis.

The variety of pain measurement scales, even greater in this review due to the variety of conditions included, such as neuropathic pain (central or peripheral), which has several domains to be assessed, or fibromyalgia, which is not listed as the main condition in any of the studies, makes it difficult to generalize the use of cannabis-derived treatments for the treatment of CP in these conditions. The potential to improve quality of life can also be mentioned, as assessed in patients with sickle cell anaemia[45], which can also be useful in the context of cancer patients and those with fibromyalgia, but there is also a need for better standardization of scales.

The size of the samples in the studies, two of which had fewer than 30 participants[28,30], was one of the biggest problems encountered, which was exacerbated by the small number of studies not reaching statistical significance in any of the outcomes assessed. In an attempt to avoid bias in small studies, a minimum of 10 participants in each intervention group was set as a criterion, as recommended for evidence in CP[33]. The small number of studies also interfered with the possibility of evaluating the results found by subgroup analysis, sensitivity and the search for publication bias.

The present study had limitations, in addition to the difficulties mentioned above, such as the impossibility of imputing data for studies with different measures of effect, reducing the number of studies; the greater presence of studies with a statistical method of complementing missing data by the last observation carried forward (LOCF), which generally results in bias due to exaggeration of the effectiveness of the intervention. There was a need

to use calculations to fill in data, which can lead to imprecision in the analysis. The influence of concomitant therapies, use of rescue drugs, interference of previous recreational use on positive or adverse effects by variety or failure to be reported, interfered with the measurement and control of these variables.

Other systematic reviews have been carried out measuring the effect of cannabis-derived treatments for various etiologies, and in general the data is conflicting as to whether it is suggested as an alternative treatment for neuropathic pain[47], fibromyalgia and rheumatoid arthritis[17], or whether it is effective for the treatment of CP of neuropathic origin[48]; in addition to there being a shortage of unbiased, high-quality evidence for fibromyalgia[24].

As a perspective on this subject, this research proposes that there is a need for randomized double-blind studies with a larger number of participants, lasting at least twelve weeks, using outcome measures that are more relevant to clinical practice in this type of condition, data analysis using the intention-to-treat method and the possibility of comparing this therapeutic option with other already established analgesia options.

CONCLUSION

Based on the evidence evaluated, it can be concluded that among the trials analyzed, no high quality evidence was found regarding the evaluation of efficacy, safety or adverse effect outcomes related to the use of cannabis-derived treatments in the management of CP, and no recommendations or restrictions on these aspects can be produced. Thus, the use of cannabis-derived treatments for CP requires a careful assessment of each individual situation, such as considering refractoriness to conventional and more established therapies or the possibility of combining these with cannabis-derived treatments.

There is a need for randomized double-blind studies with a larger number of participants, lasting at least 12 weeks, using outcome measures that are more relevant to clinical practice in this type of condition, analysis of data using the intention-to-treat method and the possibility of comparing this therapeutic option with others that have already been established.

AUTHORS' CONTRIBUTIONS

Dorgival Nafs Pinto da Silva Lopes-Júnior
Statistical Analysis, Data Collection, Research, Methodology, Writing - Preparation of the Original, Visualization.
Breno de Medeiros Bonfim
Statistical Analysis, Data Collection, Research, Methodology, Writing - Preparation of the Original.
Ricardo Wagner Gomes da Silva-Neto
Writing - Review and Editing, Supervision, Visualization.
Alexandre Magno da Nóbrega Marinho
Project Management, Methodology, Writing - Review and Editing, Supervision, Visualization.

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