Effects of cannabinoids on pain control, quality of life and opioid-sparing in cancer patients: systematic review

Utilização de canabinoides no controle da dor, na qualidade de vida e no efeito poupador de opioides em pacientes com câncer: revisão sistemática

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ABSTRACT

BACKGROUND AND OBJECTIVES: Cannabinoids, such as delta-9-tetrahydrocannabinol and cannabidiol, have several therapeutic properties that may be useful in medicine. The objective of this study was to analyze the impact of cannabinoid use on pain control, quality of life and opioid-sparing in patients with advanced cancer.

CONTENTS: A systematic review of the evidence for the use of cannabinoids in patients with advanced cancer was conducted on 1) Pain control; 2) Quality of life; and 3) Opioid-sparing effect. PubMed, Web of Science and Cochrane databases were searched for articles, written in English, published between January 1, 2011, and December 31, 2022, with the filters "randomized controlled trials" and "clinical trials". Using oral formulations of cannabinoids was accepted as "intervention" and placebo as "control". Risk of bias analysis was performed with Cochrane's RoB 2 and ROBINS-I tools. This review followed the 2020 PRISMA-statement. Ten studies were included, with 1169 participants, most with moderate risk of bias. The studies were from Australia (n=4), Canada (n=1), Israel (n=1), Mexico (n=1), The United Kingdom (n=1); two were multinationals. Eight were randomized, placebo-controlled trials; two were non-randomized studies. The most used formulation was nabiximols oral spray. Cannabinoids provide a clinical improvement in pain control. Evidence of improved quality of life with cannabinoids is inconclusive. Cannabinoids do not affect the daily dose of opioids in refractory cancer pain. Cannabinoid use cannot be said to have an opioid-sparing effect.

CONCLUSION: It is necessary to expand research on the prescription of cannabinoids in individuals with cancer and other progressive diseases, with several comorbidities and multiple medications, in different health contexts.

Keywords: Analgesics, Cancer, Cancer pain, Cannabinoids, Opioid, Palliative care, Quality of life.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Os canabinoides, como o delta-9-tetrahidrocanabinol e o canabidiol, possuem propriedades terapêuticas que podem ser úteis em pacientes oncológicos. O objetivo deste estudo foi avaliar o impacto do uso de canabinoides no controle da dor, na melhoria da qualidade de vida, e no efeito poupador de opioides em pacientes com câncer avançado.

CONTEÚDO: Realizou-se uma revisão sistemática sobre a evidência da utilização de canabinoides em pacientes com câncer avançado, relativamente a: 1) Controle da dor; 2) Qualidade de vida; e 3) Efeito poupador de opioides. Foram buscados artigos na Pubmed, *Web of Science* e Cochrane, em inglês, publicados entre 2011 e 2022, com os filtros "randomized controlled trials" e "clinical trials". Aceitaram-se como "intervenção" qualquer uso de formulações orais de canabinoides e como "controle" o uso de placebo. Fez-se análise de viés com as ferramentas da Cochrane RoB 2 e ROBINS-I. Seguiu-se a Declaração PRISMA 2020. Foram incluídos 10 estudos, com 1169 participantes, a maioria com risco moderado de viés. Os estudos provinham de Austrália (n=4), Canadá (n=1), Israel (n=1), México (n=1), Reino Unido (n=1); dois eram multinacionais. Oito eram ensaios randomizados controlados com placebo; dois eram não randomizados. A formulação mais usada foi *spray* bucal de nabiximóis. Os canabinoides proporcionam uma melhoria clínica do controle da dor. A evidência da melhoria da qualidade de vida com canabinoides é inconclusiva. Os canabinoides não afetam a dose diária de opioides na dor oncológica refratária. Não se pode afirmar que o uso de canabinoides tem um efeito poupador de opioides.

CONCLUSÃO: É necessário incrementar a investigação sobre a prescrição de canabinoides em indivíduos com câncer e outras doenças progressivas, com comorbilidades e polimedicação, em diferentes contextos de saúde.

Descritores: Analgésicos, Canabinoides, Câncer, Cuidados paliativos na terminalidade da vida, Dor do câncer, Opioides, Qualidade de vida.

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HIGHLIGHTS

- There is evidence of clinical improvement in pain control with cannabinoids.
- The evidence for improved quality of life with cannabinoids is inconclusive; however, cannabinoids do not impair quality of life in cancer patients.
- There is no evidence that cannabinoids have an opioid-sparing effect in patients with cancer pain.

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INTRODUCTION

Chronic pain (CP) affects more than 30% of people worldwide[1], representing a huge personal and economic burden, and is a common reason for seeking medical attention[2].

Opioids are commonly prescribed for chronic pain[3]; however, they only provide benefits for certain patients. A study[4] containing 96 studies found high-certainty evidence that, compared to placebo, opioids provide significant pain relief for 12% of patients for whom opioids are prescribed. In addition, opioids are associated with adverse effects that depend on the dose[5]. There is considerable interest in therapies that can enable CP patients taking opioid therapy to reduce the doses needed to treat pain. One promising approach is to add cannabis therapy, which scientific evidence suggests may be equally effective to opioids in reducing pain and improving physical functioning among people living with chronic pain[4]. Experimental studies have shown that opioids and cannabis have similar signal transduction systems[6], and observational studies have shown that opioid-related mortality rates decreased after the legalization of cannabis[7,8].

The cannabis sativa plant contains almost 500 bioactive compounds, with more than 140 different cannabinoids[9]. The most widely studied cannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), with THC being the most psychoactive and euphoric component[10]. The benefits of these compounds include analgesia, anti-emesis, muscle relaxation, improved quality of life (QoL), among others [9]. Adverse effects can be overcome clinically with a gradual titration of THC[11]. CBD is less toxic, even at high doses, and has anxiolytic, antipsychotic, anti-inflammatory, antioxidant, anticonvulsant and neuroprotective effects[12]. It is thought that CBD can reduce the adverse psychotropic effects of THC[13]. Cannabis sativa preparations with a standardized extract of THC and CBD are called nabiximols[14].

Among cannabinoids, there is uncertainty about the best product/combination to control a specific symptom, route of administration and best dosage[15]. It is unknown whether the type/dose of cannabinoid suitable for one clinical situation can also be applied in another[9]. There are concerns about safety and interaction with other drugs, especially because of the synergism between cannabinoid and opioid receptors in the antinociceptive system[16]. The opioid-sparing effect (OPE) provided using medical cannabis for CP remains uncertain. Between 64% and 77% of CP patients who responded to cross-sectional surveys reported a reduction in long-term opioid use after adding medical cannabis to their treatment[17,18]. A systematic review concluded that preclinical studies provided robust evidence for the opioid-sparing effects of cannabis[19].

The aim of this study was to evalu"te t'e Impact of cannabinoid use on pain control, QoL improvement and the opioid-sparing effect in patients with advanced cancer.

CONTENTS

This study looked at the evidence for the use of cannabinoids in patients with advanced cancer, in relation to: 1) pain control; 2) QoL; and 3) OPE. Searches were carried out in Medline/Pubmed, Cochrane and Web of Science. The last search took place on January 3, 2023.

The following terms were used: "Cannabinoid*" AND ("Cancer" OR "Neoplasm* OR "Antineoplastic Agents") AND ("palliative care" OR "refractory" OR "Advanced"), identified in the Titles and Abstracts. The following filters were used: "randomized controlled trials", "clinical trials". We searched for articles in English, published between January 1, 2011 and December 31, 2022. No manual search was carried out.

The inclusion criteria were: adult patients (≥18 years) with advanced cancer. Interventions - all medical prescriptions for cannabinoids, in various formulations (mouth sprays, oral capsules, oil solutions). Comparators - any, especially placebo. Outcomes - pain control; QoL; OPE. All the studies had more than 10 participants and used validated, internationally recognized scales/questionnaires.

From the articles found, the following were excluded: repeated articles; different types of study; different interventions; small sample size; pre-clinical trials; different population; and hidden cannabinoid dose. The titles of the articles were screened by the first author. Articles deemed eligible were selected for full analysis by two independent reviewers (SS, PRP). In the event of disagreement over inclusion/exclusion, a consensus was reached by dialog. The extracted data was compared, and any discrepancies were resolved by consensus. All the articles included explained the protocol applied, how the results were collected, and the methodologies involved.

The full text of the articles was assessed for eligibility criteria by two independent researchers (SS, PRP). The authors of the articles were not contacted for further information. No automation tools were used.

Data list

Data was sought for the three outcomes: pain control, QoL, OPE. The articles included had to address at least one of the outcomes.

Data was also searched for other variables: authors and country of origin; year of publication; study design; study objectives; site and sample; type of intervention; control group; main outcomes; observations.

Assessment of the risk of bias in studies

The randomized and non-randomized studies were assessed using the Cochrane RoB 2, [20] and ROBINS-I,[21] tools, respectively.

Effect measures

In the studies that compared cannabinoids and placebo, the results were measured by comparing the start and end of the intervention in both groups, with p-value being used as the main measure of effect.

In the studies that presented results after treatment with cannabinoids, the measures of effect used were mainly differences in means or percentage differences.

Due to the small number of studies and their heterogeneity, it was decided not to carry out a meta-analysis. A qualitative analysis of the studies was carried out.

In order to better synthesize the information, it was decided to group the results according to the outcomes: 1) Pain control; 2) QoL; and 3) OPE.

RESULTS

Initially, 172 articles were found. After removing duplicates, 145 articles were examined based on title/abstract, eliminating 92. Of the remainder, articles were excluded due to: different types of study (n=16); different interventions (n=12); few participants (n=4); pre-clinical trials (n=4); different population (n=3); hidden cannabinoid dose (n=1). Ten articles were included.

The selection process was described in the flow diagram[22] shown in figure 1.

Study characteristics

Ten articles were included with a total of 1169 participants, with average ages between 55 and 67. The studies came from five continents, some of which were multinational: Oceania (n=4), Europe (n=3), America (North, n=3; South, n=2), Asia (n=1) and Africa (n=1).

The characteristics of the studies in this review are shown in table 1.

Randomized controlled trial (RCT) [23] with 144 patients with advanced cancer to evaluate the efficacy of CBD on symptom control, QoL, safety and OPE. The intervention group was prescribed an oral solution of CBD oil (100 mg/ml); the control group was prescribed placebo. There was dose titration for 14 days and maintenance until 28 days[23].

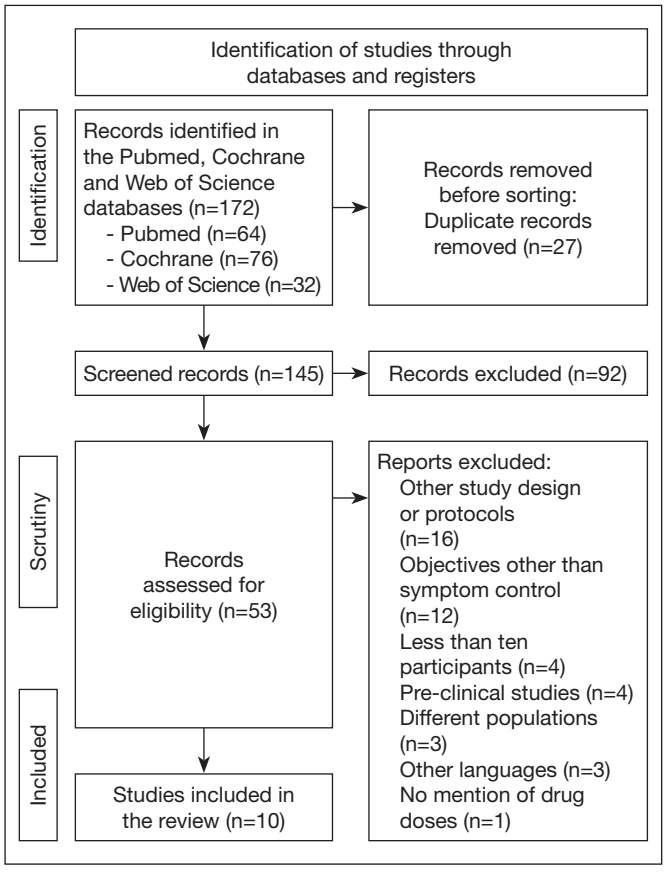

Figure 1. Flowchart of the search and selection process.

Clinical trial with 25 patients with advanced cancer,[24] to evaluate the analgesic efficacy of THC/CBD, QoL and safety. The intervention group was prescribed THC/CBD mouth spray (1.25mg/1.25mg in one spray); the control group was prescribed placebo. Doses were titrated for nine days, maintained for 10-15 days and followed up for the next 16-30 days[24].

Another RCT with 81 patients[25] with cancer at any stage, receiving intravenous chemotherapy. The aim was to evaluate the effect of THC/CBD on nausea and vomiting, QoL and safety. The design included three cycles: 1st cycle (1-4 capsules 8/8h of THC 2.5mg/CBD 2.5mg, orally); 2nd cycle (placebo), crossing participants; and 3rd cycle (the participant chose their favorite cannabinoid or placebo). Cycles 1+2 were completed by 72 participants[25].

An open, two-arm, prospective trial[26] with 21 patients with metastatic or locally advanced cancer. The aim was to assess the effect of cannabinoids on symptom control, QoL, OPE and safety. One group was prescribed an oral solution of CBC oil (100mg/mL) and the other a solution of THC oil (10mg/mL). Doses were increased according to protocol, then maintained for 14, ideally 28 days[26.]

Clinical trial with 24 cancer patients[27] (87.5% were undergoing chemotherapy) to assess the effect of THC/CBD on appetite, QoL and safety. THC/CBD oral capsules (9.5mg/0.5 mg) were prescribed 12/12h for six months[27].

Multicenter (phase III) RCT[28] with 380 patients with advanced cancer and CP refractory to opioids. The aim was to evaluate the effect of nabiximols on symptom control, QoL and OPE. The intervention group was prescribed nabiximols mouth spray (THC 27mg/ml + CBD 25mg/mL), the control group was prescribed placebo mouth spray. The doses were titrated up to 14 days and maintained for three weeks[28].

Another pilot RCT, [29] with 65 lung cancer patients, 47 of whom were randomized. The aim was to assess the effect of nabilone on weight, symptom control, QoL, anthropometric and biochemical variables. Oral capsules of nabilone (0.5mg) or placebo were prescribed. Doses were titrated up to 1mg for six weeks[29].

In the UK, they carried out an open,[30] follow-up, multicenter trial with 43 patients with advanced cancer, with refractory pain under opioids, to evaluate the effect of cannabinoids on pain, QoL and safety. One group was medicated with a nabiximol mouth spray (THC 27mg/mL and CBD 25mg/mL), the other with a THC 27mg/mL mouth spray. The average duration of treatment for THC/CBD was 25 days, for THC it was 151.5 days[30].

An international collaboration[31] carried out an RCT with 360 patients with advanced cancer and opioid-refractory pain to evaluate the effect of nabiximols on symptom control, QoL and safety. Patients were medicated with nabiximols mouth spray (THC 27mg/ml and CBD 25mg/ml) or placebo spray. There was a baseline period of 5-14 days, followed by five weeks with titration and treatment (in four groups, with three doses). Maximum study duration was nine weeks[31].

Table 1. Main characteristics of the included studies (n=10)

Authors and Country	Type of study	Objective	Population	Formulation of Cannabinoids	Intervention	Control	Observations
Hardy et al.[22] Australia	RCT (dose--escalated placebo, phase IIb).	Determine whether CBD oil can improve symptomatic distress in patients with advanced cancer receiving palliative care.	n=144 (52.8% men, age 64.6±12.8 years); advanced cancer (prostate 21.1%, breast 15.5%, colorectal 14.8%, gynecological 12.7%, pulmonary 9.2% and hematological 4.9%); patients received palliative care.	CBD oil solution (100 mg/mL) oral.	Dose titration 3/3 days: from 0.5mL 1x/day to 2mL 3x/day for 14 days, according to tolerability. Participants remained on the titrated dose until 28 days.	Placebo	Scales: ESAS; SGIC. Under treatment with opioids.
Clarke et al.[24] Australia	Clinical trial	Assess the safety, tolerability, pharmacokinetics and analgesic effect of a new medicinal cannabis spray in patients with incurable cancer and pain uncontrolled with opioids.	n=5 in Stage I (which does not fulfil the eligibility criteria for this study). n=25 in Stage II (which is considered in this study); patients (60% women; age 55.9±11.9 years); advanced cancer (28% breast, 16% lung and gastrointestinal, 12% hematological, 8% pancreas and ovaries, 4% melanoma, prostate and central nervous system).	THC/CBD mouth spray (1.25mg/1.25mg per spray).	Stage I: 1 day with 2 sprays, next day with 6 sprays. Stage II: 1-9 days of dose escalation (1 spray 3 days; 2 sprays 3 days; and 3 sprays 3 days); 10-15 days of treatment with the dose tolerated in the previous stage; 16-30 days of follow-up.	-	Scale: EORTC-QLQ--C30-v3 Single-arm study, unblinded for researchers and participants.
Grimison et al.[25] Australia	RCT (multicentre, double--blinded, placebo, phase II/III).	Assess an oral cannabis extract (THC:CBD) for the prevention of refractory nausea and vomiting induced by chemotherapy.	n=81 (78% women; ages: 18-49 years -30%, 50-69 - 63%, ≥70 years - 6%); cancer at any stage (breast 33%, colorectal 13%, lung 12%, esophageal/gastric 9%, gynecological 9%, pancreatic 9%, hematological 4%, testicular 4%).	THC/CBD oral capsules (2.5mg/2.5mg).	1st cycle: 1-4 self-titrated capsules 3 times a day, starting 1 day before intravenous chemotherapy, ending on day 5; 2nd cycle: placebo (cross-over between participants); 3rd cycle: treatment preferred by the participants.	Placebo	Various centers: New South Wales. 72 participants completed cycles 1 and 2. Scale: AQOL-8D.
Good et al.[26] Australia;	Prospective two-arm open label trial of escalating doses.	Assess the response to medicinal cannabis, determine tolerated median doses of CBD and THC and document adverse events.	n=21 (66.7% women, age 57.5±12.4 years); metastatic or locally advanced cancer (breast 33%, prostate 19%, colorectal 14%, gynecological 10%, pancreas 10%, bone and soft tissue 5%, hematological 5%).	Oral solution of CBC oil (100mg/mL) and THC (10mg/mL).	1 dose with CBC (50-600mg/day), the other with THC (2.5-30mg/day). Increases every 2/2 days, until symptomatic control or unacceptable side effects. Then the dose was maintained for 14, ideally 28 days.	-	Scales: CGIC, DASS-21, EORTC-QLQ-C-15-PAL, ESAS, PGIC. Participants were taking opioid therapy.
Bar-Sela et al.[27] Israel	Clinical Trial	Asses the effect of dose--controlled cannabis capsules on anorexia-caquexia syndrome in patients with advanced cancer.	n=24 (62.5% men, average age 66 years); Most common cancers: pancreatic, colon, prostate and lung carcinoma.	THC/CBD oral capsules (9.5mg/0.5mg).	1 capsule 12/12h for 6 months. If adverse effects occur, reduce the dose by half.	-	Scale: EORTC-QLQ-C30. -87.5% of the participants were undergoing chemotherapy.
Lichtman et al.[28] Several countries	RCT (multi-center, double--blind, placebo, phase III).	Asses the efficacy of nabiximols as adjuvants in advanced cancer patients with chronic pain unrelieved by optimized opioid therapy.	n=380 (men/age: experimental group 55.8%/59.2±12.0 years; control group 52%/ 60.7±11.1 years); advanced cancer (lung 16.9%, breast 15.6%, colon 10.8%, prostate 9.8%, hematological 6.0%, pancreas 5.8%, head and neck 5.5%); Patients with chronic pain refractory to optimized opioid treatment.	THC|CBD mouth spray (27mg/mL|25mg/mL).	On the 1st day, 1 spray, gradually increasing until: acceptable pain relief, unacceptable adverse effects, or maximum of 10 sprays/day. Complete titration at 14 days; then maintain for 3 weeks.	Placebo	114 centers from Belgium, Bulgaria, the Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, Romania, the United Kingdom and the United States of America took part. Scales: PGIC, PSQ, SGIC.

Continue...

Table 1. Main characteristics of the included studies (n=10) – continuation

Authors and Country	Type of study	Objective	Population	Formulation of Cannabinoids	Intervention	Control	Observations
Turcott et al.[29] México	RCT (pilot, double-blind, placebo).	Asses the effect of nabilone vs. placebo on appetite, nutritional status and QoL in patients with advanced lung cancer.	n=65; 47 were randomized (women/age: experimental group 78.9%/61.1±10.6 years; control group 78.6%/52.6±11.8 years); advanced non-small cell lung cancer.	Oral capsules of synthetic THC (nabilone 0.5mg).	1 capsule/day for 2 weeks, then 2 capsules/day for 6 weeks.	Placebo	Scales: EORTC-QL-Q-C30, EORTC-QL-Q-LC13, FAACT, PG--SGA. Participants with a good performance status and with anorexia.
Johnson et al.[30] United Kingdom	Long-term, open-label, follow-up study.	Investigate the long-term safety and tolerability of THC/CBD spray and THC spray for pain relief in patients with advanced cancer.	n=43 (men/age: THC/CBD group 59%/ 57.5±13.5 years; THC group 25%/ 58.6±6.3 years); advanced cancer (breast 21%, prostate 16%, rectum 16%, lung 7%, bone 5%); Patients with pain refractory to optimized opioid treatment.	Spray bucal de THC|-CBD (27mg/mL|25mg/mL) (n=39); e Spray bucal de THC 27mg/mL (n=4).	Patients who had previously participated in the 2-week RCT. Self-titration. Visits: at the end of the RCT/screening; after 7-10 days; after 4/4 weeks; at study completion/dropout.	-	Centers: 21 in the UK and 1 in Belgium. Scales: BPI-SF, EORTC-QLQ-C30. Average duration of treatment: for THC/CBD - 25 days, for THC - 151.5 days. Participants taking opioid treatment.
Portenoy et al.[31] Several Countries	RCT (double-blind, placebo graded dose).	Obtain information on the dose response to analgesia and the safety of nabiximols in a population with cancer and pain not controlled with opioids.	n=360 (51.7% men, age 58±12.2 years); advanced cancer (gastrointestinal 17.8%, lung 17.8%, breast 15%, prostate 12.2%); patients with pain refractory to optimized opioid treatment.	Spray bucal de THC|-CBD (27mg/mL|25mg/mL); número de pulverizações: dor ligeira: 1-4; dor moderada: 6-10; dor intensa: 11-16.	A baseline period of 5-14 days, followed by 5 weeks, with titration and treatment (in 4 groups, with 3 doses). After 2 weeks, a post-study was carried out. Maximum duration of 9 weeks.	Placebo	A total of 84 centers in North and South America, Europe and South Africa participated. Scales: BPI-SF, EORTC-QLQ-C30-v3, MADRS, PGIC.
Brisbois et al.[32] Canadá	RCT (pilot, double--blind, placebo, phase II).	Determine whether THC can improve the taste and perception of smell, appetite, calorie intake and QoL of cancer patients with chemosensory alterations.	n=21 (men/age: experimental group 64%/ 67.0±10.9 years; placebo group 50%/ 65.5+8.0 years); advanced cancer (THC/placebo: lung 45%/50%, genitourinary 27%/20%, gastrointestinal 18%/10%); patients with anorexia and chemosensory alterations.	Cápsulas orais de THC 2,5mg.	Treatment: Days 1-3, 1xday; Days 4-18, 3xday; with the option of increasing the dose up to 20mg/day.	Placebo	Scales: ESAS, FAACT. Around 33% of patients received chemotherapy.

AQOL-8D = Assessment of Quality of Life-8 dimensions; BPI-SF = Brief Pain Inventory Short-Form; CBD = Cannabidiol; CGIC = Clinician Global Impression of Change Scale; DASS-21 = Depression, Anxiety, and Stress Scale; EORTC = European Organization for Research and Treatment of Cancer; ESAS = Edmonton Symptom Assessment System; FAACT = Functional Assessment of Anorexia/Cachexia Therapy questionnaire; MADRS = Montgomery-Asberg Depression Rating Scale; PGIC = Patient Global Impression of Change scale; PG-SGA = Subjective global assessment; PSQ = Patient Satisfaction Questionnaire; QoL = Quality of Life; QLQ-C15-PAL = Quality of Life Questionnaire Core 15 Palliative scores; QLQ-C30-v3 = Quality of Life Questionnaire, version 3; QLQ-LC13 = Quality of Life Questionnaire for Lung Cancer; RCT = Randomized Controlled Trial; SGIC = Subject Global Impression of Change; THC = Delta-9-Tetrahidrocanabinol.

A pilot RCT (phase II)32 with 21 patients with advanced cancer (33% receiving chemotherapy) to assess the effect of THC on taste and odor perceptions, appetite, caloric intake, QoL and safety. The intervention group was prescribed oral capsules of THC 2.5mg; the control group was prescribed placebo. The duration was 18 days, with doses titrated up to 20mg a day[32].

Risk of bias in studies

The risk of bias of randomized and non-randomized studies is shown in figures 2 and 3, respectively. Most of the studies had a moderate risk of bias. Three studies had domains with a high risk of bias.

One particular study took place over three cycles, which were not differentiated when the results were presented. In the last cycle, most of the participants opted for the same treatment arm, which may have had an impact on the results; therefore, domain 4 was considered to be a high risk of bias[25].

In the study by authors[27], domain 5 was classified as high risk of bias, as many participants were lost: there were 24 participants at the start in both groups, with only six completing the treatment. This study had a high risk of bias overall.

In Johnson et al. domain 5 was considered to have a high risk of bias because, of the 43 participants followed, only one remained until the end. Dropouts were for various reasons, mostly (n=24) due to adverse effects. Overall, the risk of bias was high[30].

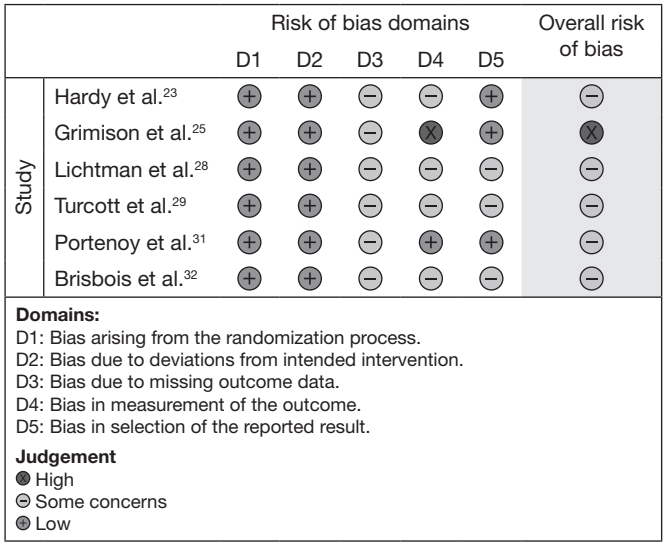

Figure 2. Risk of bias of randomized studies (n=6)

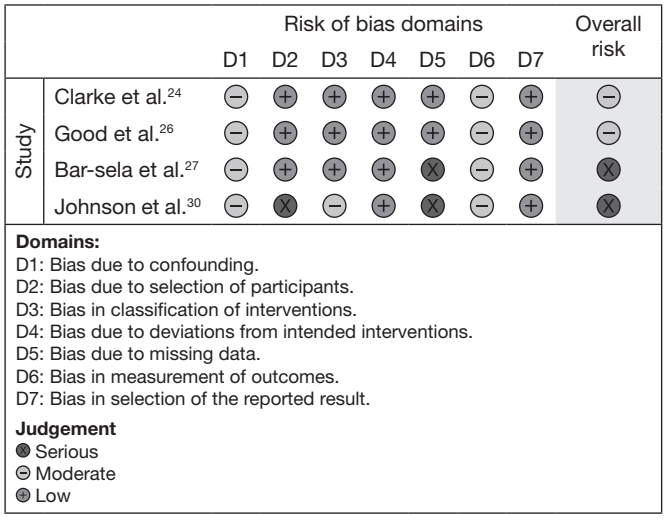

Figure 3. Risk of bias of non-randomized studies (n=4)

Results of individual studies

A summary table was drawn up with the main findings and differences between the studies (Table 2). Next, the findings are presented according to the proposed outcomes.

Pain control

Pain was one of the symptoms most addressed in seven of the 10 articles included in this review, five of which were RCTs.

In the study[28] there were differences in terms of improvement in the percentage of average pain from the start of the intervention to the end in the "intention-to-treat" population (p=0.09). There was no difference between nabiximols and placebo in terms of "average pain" and "worst pain" (p=0.25 and p=0.68, respectively)[28]. However, considering the percentage improvement in mean pain from the start of treatment to the end in the "per-protocol" population, there was an improvement in pain in favor of nabiximols (p<0.05). In this multicenter study, it was also found that the population of the United States of America showed all the most favorable results, compared to the population of European countries[28].

Another study evaluated: 1) different doses of nabiximols: low, medium, and high, compared to placebo; and 2) all doses combined, compared to placebo[31]. Regarding the proportion of participants with 30% pain relief, there was no significance (p=0.59). The results were found to be clinically in favor of nabiximols, but only considering the low and medium doses, versus placebo, although without statistical significance. Looking at the whole spectrum of responses (from 0 to 100%), there was already an improvement (p<0.05); however, when the different dosages were analyzed, it was clear that the results were only due to the low and medium doses (p=0.01 and p<0.05, respectively) and, in terms of the response of improvement in average daily pain, only the group given low doses benefited (p<0.01). At the end of treatment, in terms of average daily "worst pain", a difference was evident for low-dose nabiximols (p<0.05), with medium and high doses showing a greater reduction than placebo, but not a significant one[31]. There was a clinical improvement in the pain severity indices for the low, medium, and high doses, but this was not significant (p=0.24, p=0.12 and p=0.86, respectively). Regarding pain interference indices, there was clinical improvement at the low and medium doses, while at the high dose the treatment was not in favor of nabiximols (p=0.87, p=0.09, p=0.9, respectively)[31].

In another research using CBD, pain was measured numerically from zero to 1023. There were no differences at day 14 (p=0.25) or day 28 (p=0.54). When pain was assessed as a QoL parameter, despite the clinical improvement, there was no relevant difference (p=0.26).[23] In another multicenter RCT[25], the association THC/CBD versus placebo improved pain in cancer patients,

Table 2. Analysis of differences between individual studies (n=10)

Authors	With differences either 1) between the start and end of the study in the cannabinoid group; or 2) between the cannabinoid and control groups	No differences either 1) between the start and end of the study in the cannabinoid group or 2) between the cannabinoid and control groups.
Hardy et al.[23]	Patients reported feeling better at 28 days (70% CBD, 64% placebo).	Proportion of responders (p=0.13). Effect of CBD on change in pain (p=0.26), physical functioning (p=0.77), and QoL (p=0.70). Patient global impression of change at 7, 14, 21 and 28 days (p=0.54; p=0.19; p=0.38; p=0.50; respectively). There was no correlation between the dose of CBD selected by the participant and the dose of opioid. The "oral morphine equivalent" dose had no differences at 14 days (p=0.10) and 28 days (p=0.39). Change between arms at 14 and 28 days in the individual pain component (p=0.25 and p=0.54, respectively)
Clarke et al.[24]	Individual parameters of the EORTC-QLQ-C30: Pain (p<0.001 breast and prostate cancer, and p=0.009 in the remaining cancers); Emotional functioning (p=0.004) only in breast and prostate cancer patients.	Overall improvement in QoL, but not statistically significant (p=0.13 for breast and prostate cancer, p=0.44 for other cancers, respectively). In the other parameters of the EORTC-QLQ-C30, there were no statistically significant differences when comparing breast/prostate cancer and other cancers.
Grimison et al.[25]	EORTC-QLQ-C30 parameters: Global QoL (p=0.019); Pain (p=0.003); Physical overdimension (p<0.001).	Complete response and no significant nausea (p=0.12). EORTC-QLQ-C30 parameters: independent living, happiness, coping, relationships, self-esteem, senses and mental overdimension (p=0.13; p=0.50; p=0.67; p=0.1; p=0.07; p=0.18 and p=0.27, respectively).
Good et al.[26]	Reduction in the daily dose of morphine equivalents from the start of the study (median 100mg, range 0-420) to the end (95mg, range 0-370) (p=0.09). Median scores for depression (p=0.04) and stress (p=0.046) on day 14.	There were no significant changes in pain; in overall symptom burden (9 symptoms, including pain); and in the set of physical symptoms (including pain), between the beginning and the 14th day of treatment (p>0.05; p=0.11; and p=0.65; respectively).
Bar-Sela et al.[27]	-50% of patients with pain reduction at six months.	No change in QoL (EORTC). No reduction in pain: at 2 weeks; between 2 weeks and 4.5 months.
Lichtman et al.[28]	Percentage improvement in "average pain" in the "per-protocol" population (p=0.0378); Subjective impression of global change and patient satisfaction at week 3 (p=0.0024 and p=0.0001, respectively);	Mean pain and worst pain (p=0.253 and p=0.678, respectively). Regular opioid dose, opioid rescue dose and total daily opioid dose (p=0.6410, p=0.4217, p=0.9328). Percentage improvement in "average pain" in the "intention-to-treat" population (p=0.0854) Percentage improvement in average pain in the "per-protocol" population in Europe (p=0.3902). Subjective global impression, patient global impression of change and patient satisfaction at last visit (p=0.0521, p=0.0861, p=0.0836).
Turcott et al.[29]	QoL between the start and after eight weeks of treatment: role functioning (p=0.030), emotional functioning (p=0.018), social functioning (p= 0.036) and insomnia (p=0.020).	No change in pain after eight weeks (p=0.06)
Johnson et al.[30]	Sustained improvement in the "worst pain" and "pain severity" averages from the beginning to the end of the study. 24% reduction in pain (on the EORTC) from start to week 5.	No differences in the EORTC, except for the worsening of "physical functioning" with cannabinoids.
Portenoy et al.[31]	Overall analgesic response (p=0.035), with more favorable results in the low and medium doses of cannabinoids (p=0.008 and p=0.038). Change in "average pain" in the lowest dose subgroup (p=0.006) and, combining the low+medium dose subgroups (p=0.019). Mean change in "worst pain" (p=0.047), with better results at the low dose (p=0.011). Reduction in weekly "average pain", which was better at week 5 at the low dose (p=0.024). "Composite measure of opioids" at the low and low/medium doses of cannabinoids combined (p=0.038 and p=0.05).	>30% reduction in mean pain score (p=0.059). Continued response to high dose cannabinoids (p=0.68). Change in "moderate pain" in the subgroups with medium and high doses of cannabinoids (p=0.187 and p=0.750). Mean change in "worst pain" in the medium and high doses of cannabinoids (p=0.397, p=0.829). Regular opioid dose and rescue opioid dose (p>0.05). "Opioid composite measure" (pain reduction with opioid reduction or vice versa) considering all cannabinoid doses (p>0.05).
Brisbois et al.[32]	-Improved QoL between the beginning and end of the study in the THC group (p=0.026). Improved relaxation (p=0.046), sleep (p=0.043) and appetite (p=0.05).	Global QoL scores improved in both groups (p=0.704).

CBD = Cannabidiol; EORTC = European Organisation for Research and Treatment of Cancer; QoL = Quality of Life; QLQ-C15-PAL = Quality of Life Questionnaire Core 15 Palliative scores; QLQ-C30 = Quality of Life Questionnaire version 3; THC =- Delta-9-Tetrahidrocanabinol.

with relevance (p<0.01). In the study.[29], between the start and end of treatment with nabilone (synthetic THC), there were differences in terms of pain as an element of QoL (p<0.05), which was not the case with placebo (p=0.36).

Two non-comparative studies evaluated the use of cannabinoids in pain. One of them, with THC/CBD, showed significant pain relief (as an element of QoL) (p<0.001 for breast and prostate cancers, and p<0.01 for other cancers) [24]. However, with another evaluation method, they measured: 12% improvement in pain initially, 30% in the post-treatment phase, with a subsequent worsening of 13% compared to baseline after the follow-up phase (in which the cannabinoid was discontinued)[24]. The study[30] analyzed pain scores, recording a decrease compared to baseline in scores at all observation times for average pain (~5.5 to ~4.5 on the scale used), pain severity (~5.5 to ~4.0) and worst pain (~7.5 to ~6.0), with improvements of 24% (as a QoL parameter). There was an improvement in terms of pain, although the researchers felt that the participants' pain control was suboptimal. Regarding the interference of pain in daily life, pain worsened in the first week and improved again in the fifth week, but still worsened compared to the start of treatment (~6.5 to ~5.5)[30].

Quality of life

In all the studies, QoL was assessed in some way.

In the study[28], which used nabiximols, results were measured on the basis of: 1) global perception of change questionnaires by the clinician, 2) by the participant, and 3) a global patient satisfaction questionnaire, measured at the third week of follow-up (p<0.05, p=0.10, p=0.0001, respectively), at the fifth week (p<0.01, p<0.05, p<0.05) and at the last visit (p<0.01 p=0.09, p=0.08, respectively). The results tended towards clinical and individual improvement with nabiximols at the last visit[28].

In the study[31], also using nabiximols, there was similarly no relevance in the overall impression of change felt by the participant (regardless of the low, medium or high dose used) at the end of treatment (p=0.27; p=0.66; p=0.54 respectively). However, a small effect in terms of treatment improvement was observed in most of the QoL subscales. In the study[32] with THC, overall QoL was assessed, and there was an improvement, but no significant difference compared to placebo (p=0.70). In the study[23] using CBD, there were no differences in symptom burden, either at 14 days (p=0.98) or 28 days (p=0.36). In fact, in both arms the participants reported feeling better, but in a higher percentage in the placebo group (65%) than in the CBD group (53%).

Also, in the study[25] there were no differences in QoL between the groups, specifically in relation to happiness, coping and relationships (p=0.50, p=0.67, p=0.61, respectively). However, THC/CBD capsules improved QoL based on "usefulness" (p<0.05) and the "super" physical dimension (which included items such as pain; "seeing, hearing, communicating"; and "independent living") (p<0.001). In lung cancer patients, in the study[29], when QoL was analyzed, there were better results in the placebo group than in the nabilone group, but no differences (p=0.31 and p=0.76, respectively). Despite this, the use of nabilone was associated with significant benefits in terms of social, emotional and role functioning (p<0.05 in all), which was not the case with placebo[29].

As far as non-comparative studies are concerned, there is one prospective study[26] that used one arm with CBC and the other with THC in increasing doses27. The authors[26] found a "global impression of change" reported by patients of around 44% and by doctors of 50%. However, the general assessment of QoL did not register any changes (p=0.11), nor improvements in the physical (p=0.23) or well-being (p=0.65) subscales.

The authors[27] showed that with THC/CBD there was no significant difference in QoL, but almost all their participants reported improvements in pain, fatigue, sleep quality and appetite. Also, with THC/CBD, the study[24], despite showing a clinical benefit, revealed that there was no statistical significance in overall QoL. However, there were significant differences in terms of individual QoL parameters such as role functioning, emotional functioning, fatigue, pain, insomnia and dyspnea[24]. Finally, in the open label study[30], which used THC and THC/CBD, patients' overall health status went from scores of ~31 to ~40. There were beneficial clinical differences in emotional and social functioning, a worsening in physical functioning and no changes in role functioning[30].

Opioid-sparing effect

Five of the studies examined the effect of cannabinoids on patients medicated with opioids.

In the study[28] with nabiximols, there was no significant impact on regular, rescue or total daily opioid doses (p=0.64, p=0.42, p=0.93, respectively). Nor was there any difference in the number of responders between the treatment groups (p=0.11). The authors[31] observed that patients in the nabiximols group, versus placebo, showed a better response profile to opioids (p=0.08), and only at the lowest dose of nabiximols was statistical significance obtained (p<0.05). The authors used an "opioid composite measure" which was calculated using both the change in the patient's mean pain score and the change in opioid consumption (morphine milligram equivalents). A positive response was defined as a reduction in pain with a stable or decreasing use of opioids[31]. They found this type of response only in the low and low/medium combined doses of cannabinoids (p=0.038 and p=0.05).

The study[23] found no differences in the "oral morphine equivalent" dose between CBD and placebo at 14 and 28 days (p=0.10 and p=0.39, respectively), although there was an initial drop in the opioid dose on day 14, which was not maintained on day 28 in both groups. This was the only study to analyze survival between the groups, and there were no relevant differences (p=0.22).

Two non-comparative studies also evaluated the use of opioids. The authors[26] found that at the start of treatment (with either CBD or THC) the average number of morphine equivalents was 140mg/day, decreasing to 95mg/day on day 14. Analyzing the patients who completed the 14th day of treatment, they found significant changes (p=0.09). The authors[24] confirmed that the use of THC/CBD did not lead to a sustained reduction in opioids, since on day 1 participants took a median of 60mg (45 to 170) morphine equivalents, on day 16 (end of treatment) they maintained 60mg (40 to 113) and on day 30 (end of follow-up) they rose to 63mg (32 to 128) morphine equivalents.

DISCUSSION

In this study, which aimed to evaluate the impact of cannabinoid use on pain control, QoL improvement and OPE in patients with advanced cancer, most of the studies showed that prescribing cannabinoids has the potential for benefits, with a tendency for a beneficial effect at low doses, influencing some QoL characteristics and little evidence for the issue of cannabinoids versus opioids.

In general, there is evidence of clinical improvement in pain control with cannabinoids. Sometimes in general, versus placebo[25]. In some studies, improvement in pain was an integral part of QoL[23,24,29,30]. In one RCT, there was no 30% improvement in pain with cannabinoids, but there was an improvement in the average "worst pain", versus placebo, in low doses of cannabinoids[31]. Only one RCT found no improvement in any of the variables used to measure pain with cannabinoids[28]. There is evidence in animal models supporting cannabinoid-induced analgesia[33]. In one RSL, most of the included studies demonstrated the analgesic effects of cannabinoids, although not all associations achieved statistical differences[34]. However, another RSL, which considered that it had included studies with a low risk of bias, showed that cannabinoids associated with opioids do not reduce pain in the context of cancer[35].

Three studies showed an improvement in QoL, with statistical relevance, especially in functionality[25], emotional and "role" functioning[24,29] and social functioning[29]. Three studies showed clinical improvement in QoL, but without significant differences[30-32]. Six studies showed no statistically significant differences in other dimensions of [23-27,29]. A recent RSL with meta-analysis concluded that the evidence for the use of cannabinoids in QoL is inconclusive[36].

Five articles focused on the impact of cannabinoid use on opioid therapy. In two trials, there was no significant difference in the dose of opioids with the prescription of cannabinoids (CBD in the study[23] and nabiximols in the study[28]). In the trial[26] with both CBD and THC, there was a significant reduction in the daily dose of morphine equivalents from the beginning to the end of the study (p=0.09). In the RCT[31] there was a significant reduction in the dose of opioids, but only at the low dose of nabiximols.

In the trial[24] with nabiximols, opioid doses remained unchanged during the investigation. As a result, in three studies there was no OPE, in two there was (in one of them only with low doses of cannabinoids). However, it is important to consider that most of the studies assume that they were not designed to allow this evaluation to be carried out in a fair way, since the reduction in the dose of opioids was not protocolized, or else was not recommended[28,31].

There is some evidence of OPE from cannabinoids in medication-naive mice[37]. In 2022, an RSL concluded that pre-clinical and observational studies support OPE by cannabinoids; however, it admitted that the findings of clinical trials are uncertain[38]. More research is undoubtedly needed.

This study has several limitations. Most of the studies included took place over a short period of time and with small samples. There was little inclusion of the elderly, a vulnerable population exposed to an increased incidence of cancer.

Studies with patients with "advanced cancer" were included, and the authors didn't always define whether it was local or distant, which makes a difference. In most of the studies, the outcomes were assessed in different neoplasms, and therefore with different pathophysiological mechanisms. This contributes to the heterogeneity of the results and compromises comparison.

Another limitation is that the studies included did not break down the results according to the pathophysiological component of pain. On the other hand, subjective experiences were analyzed, both in terms of pain and QoL, which are always difficult to interpret and evaluate. The studies had heterogeneous interventions, even when evaluating the same outcome.

In addition, although the same assessment scales were sometimes used, they were applied in different ways. In some studies, there was no evaluation of the effects of cannabinoids when applied in different doses; thus, there is a risk of not knowing the dosage that maximizes the beneficial effect.

In the studies that allowed concomitant analgesic therapy, this was not well defined or controlled, nor were the doses considered for a possibly fairer randomization.

CONCLUSION

This study revealed that there is a benefit in prescribing cannabinoids to control pain in patients with advanced cancer. Cannabinoids do not seem to significantly increase the overall QoL of cancer patients; however, possible positive effects are not ruled out, and there was never a worsening of QoL in the studies analyzed.

Cannabinoids, especially nabiximols, are beneficial as adjuvants to analgesia in patients with cancer pain refractory to opioids. This benefit seems to exist in clinical practice but has not always been statistically significant. Although the association is possible and beneficial, it cannot be said that the use of cannabinoids has an opioid-sparing effect.

In the future, there should be greater investment in research in this area, considering the growing increase in chronic diseases, especially cancer, whose populations have so many care needs, not always easily met by conventional treatments.

AUTHORS' CONTRIBUTIONS

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Data Collection, Conceptualization, Research, Methodology, Writing – Preparation of the original, Writing - Review and Editing, Validation, Visualization

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