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Review Article

Cannabis and Radiation Therapy: A Scoping Review of Human Clinical Trials

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ABSTRACT

Introduction: It is estimated that at least 20% of Canadian patients with cancer use cannabis to alleviate symptoms of their disease and/or cope with the side effects of their treatment. Most patients want to learn more about cannabis from their healthcare team, but most oncology professionals feel too uninformed to make recommendations. The purpose of this scoping review was to address this oncology professionals' knowledge gap, by summarizing the literature on evaluations of the benefits and harms of cannabis use before, during, or after radiation therapy (RT).

Methods and Materials: A literature search was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews guidelines, using multiple electronic databases and combinations of key terms. To be included, studies must address the use of cannabis in patients undergoing RT. In vitro and in vivo evaluations, reviews, and editorials were excluded. Eligible full text manuscripts were then subjected to a formal risk of bias assessment using the Cochrane RoB 2.0 or ROBINS-I frameworks.

Results: A total of 48 records were identified, and 8 articles were included after vetting. These 8 studies suggest that the use of cannabinoids may calm anxious patients about to start RT, reduce nausea and vomiting consistent with the contemporary standard of care, reduce the symptoms of relapse for patients with glioma, and provide symptom relief >3 years after head and neck RT but not during or immediately. Six of these studies contained a high risk of bias (eg lack of randomization, poor blinding, and subjective outcome assessments). Most studies reported mild episodes of drowsiness and dry mouth with Δ^9tetrahydrocannabinol, but substantial rates of dizziness, fatigue, and disorientation were also seen. It is important to note that these studies did not measure the impact of long-term cannabis consumption.

Conclusions: The existing body of literature evaluating the use of cannabinoids by patients undergoing RT is very limited. Well-designed randomized controlled trials are urgently needed, which address the significant design flaws of previous studies and evaluate the impact of phytocannabinoids in patients undergoing RT.

RÉSUMÉ

Introduction : On estime qu'environ 20% des patients canadiens traités pour un cancer utilisent le cannabis pour atténuer les symptômes de leur maladie ou composer avec les effets secondaires du traitement. La plupart des patients veulent obtenir plus d'information sur le cannabis de leur équipe de soins, mais la plupart des professionnels en oncologie ne se sentent pas assez informés pour formuler des recommandations. Le but de cet examen de la portée est d'aborder cet écart de savoir des professionnels en oncologie en faisant un résumé de la documentation scientifique sur l'évaluation des avantages et des inconvénients de l'utilisation du cannabis avant, pendant et après la radiothérapie.

Méthodologie et matériel : Une recherche documentaire a été effectuée selon les lignes directrices Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews, en utilisant plusieurs bases de données électroniques et combinaisons de mots-clés. Pour être incluses, les études devaient aborder l'usage du cannabis chez les patients traités par radiothérapie. Les manuscrits admissibles en plein texte ont ensuite fait l'objet d'une évaluation formelle du risque de biais en utilisant les cadres Cochrane ROB 2.0 ou ROBINS-I.

Résultats : Au total, 48 fichiers ont été identifiés, et huit articles ont été inclus après évaluation. Ces huit études suggèrent que l'utilisation du cannabis peut: calmer les patients anxieux au moment d'entreprendre la radiothérapie, réduire les nausées et les vomissements correspondant au standard de soin actuel, réduire les symptômes de récidive pour les patients atteints d'un gliome, et assurer une atténuation des symptômes >3 ans après la radiothérapie de la tête et du cou, mais pas pendant ou immédiatement après. Six de ces études

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présentaient un risque de biais élevé (p. ex., manque de randomisation, procédure d'insu inadéquate, évaluation subjective des résultats). La plupart des études rapportent des épisodes légers de somnolence, et de bouche sèche avec le 9THC, mais des taux substantiels de vertige, de fatigue et de désorientation ont aussi été constatés. Il est important de noter que ces études n'ont pas mesuré les effets à long terme de la consommation de cannabis.

Conclusions : La documentation scientifique existante sur l'évaluation de l'utilisation des cannabinoïdes par les patients traités par radiothérapie est très limitée. Des essais cliniques randomisés bien conçus sont requis de toute urgence, afin de corriger les défauts de conception des études antérieures et d'évaluer les effets des phytocannabinoïdes chez les patients traités par radiothérapie.

Keywords: Cancer; radiotherapy; cannabinoid; marijuana

Introduction

Cannabis (colloquially known as Marijuana) is a broad term used to describe organic products derived from the Cannabis plant. The unique group of active chemical compounds found in cannabis are called cannabinoids. Among the more than 100 different types of cannabinoids, the most abundant and well-studied are Δ^9tetrahydrocannabinol (9THC) and cannabidiol (CBD) [1]. THC is the primary psychoactive compound of cannabis, which is responsible for the euphoric "high" associated with cannabis use [2]. CBD is a nonintoxicating constituent of cannabis. It has been shown to counter the intoxicating effects of THC and has recently received attention for its potential therapeutic effects [2]. All forms of cannabinoids work on the endocannabinoid system within the human body, which consists of a series of neuromodulators (eg, anandamide and 2-arachidonoylglycerol) and their associated receptors located throughout the brain, peripheral nervous system, and immune system [3].

In July 2001, Canada was one of the first countries to establish federal regulations to provide access to botanical cannabis for medical purposes. This specifically included patients with cancer experiencing "severe pain, cachexia, anorexia, weight loss, and/or severe nausea" and also patients who could "demonstrate a medical need for compassionate end-of-life care" [4]. Although the benefits of cannabis for patients with cancer have yet to be rigorously established, ~20% of Canadian patients with cancer have used cannabis in the last 6 months [5], with the rate of cannabis use doubling after a cancer diagnosis [6]. Higher rates of cannabis use by patients with cancer have been reported in US states with legal recreational use [7], indicating that the current prevalence of cannabis use in Canadian patients with cancer is likely higher than that reported in prelegalization estimates.

More than 60% of patients with cancer will receive radiation therapy (RT) as part of their treatment [8]. The addition of cannabinoid therapies to RT clinical practice may carry the potential for improved healthcare outcomes for patients [3] and may also be helpful in assisting patients through intensive treatment regimen [9]. Unfortunately, most radiation therapists and oncologists are ill-prepared to support these patients, and <15% of patients with cancer receive any information about cannabis from their healthcare team [10,11]. This leaves patients undergoing RT subject to cannabis myths and misrepresentations found during internet searches [12]. The purpose of this scoping review was to address this RT health professionals' knowledge gap, by summarizing the literature on evaluations of the benefits and harms of cannabis use before, during, or after RT.

Methods and Materials

To effectively summarize findings from a heterogeneous body of knowledge, this scoping literature review was designed and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews guidelines [13].

A literature search was performed on November 29, 2019, using the following electronic databases: PubMed and CINAHL. The search used a combination of key terms; these included "marijuana" or "cannabis" or "cannabinoid" and "radiation therapy" or "radiotherapy."

To be included, empirical studies must address the use of cannabis in humans before, during, or after receiving RT for cancer. The study setting could include any country or year, as long as the articles were written in English and had the full text available. Studies that focused solely on animal or cell models were excluded. Articles that were literature reviews and expert opinions were excluded. The initial search was augmented by cross-checking the references section of relevant articles and using the "cited by" and "related articles" functions in the search engines.

The full text manuscripts for all eligible articles were then subjected to a formal risk of bias assessment using the Cochrane RoB 2.0 (for the randomized trials) or the Cochrane ROBINS-I (for nonrandomized studies) [14,15].

Results

A total of 48 records were initially identified (Figure 1). Duplicates were removed and initial screening was conducted using the title and abstract (based on the criteria described previously), leading to the inclusion of 8 articles in the review. The characteristics of these studies are summarized in Table 1. The full text manuscripts for all eligible articles were then subjected to a formal risk of bias assessment, and the findings for the various domains are summarized in Table 2 and discussed in detail in the following.

One study evaluated the use of cannabinoids to improve mood in anxious patients about to receive RT. Davies et al [16] evaluated the use of 10 mg synthetic Δ^1-trans-

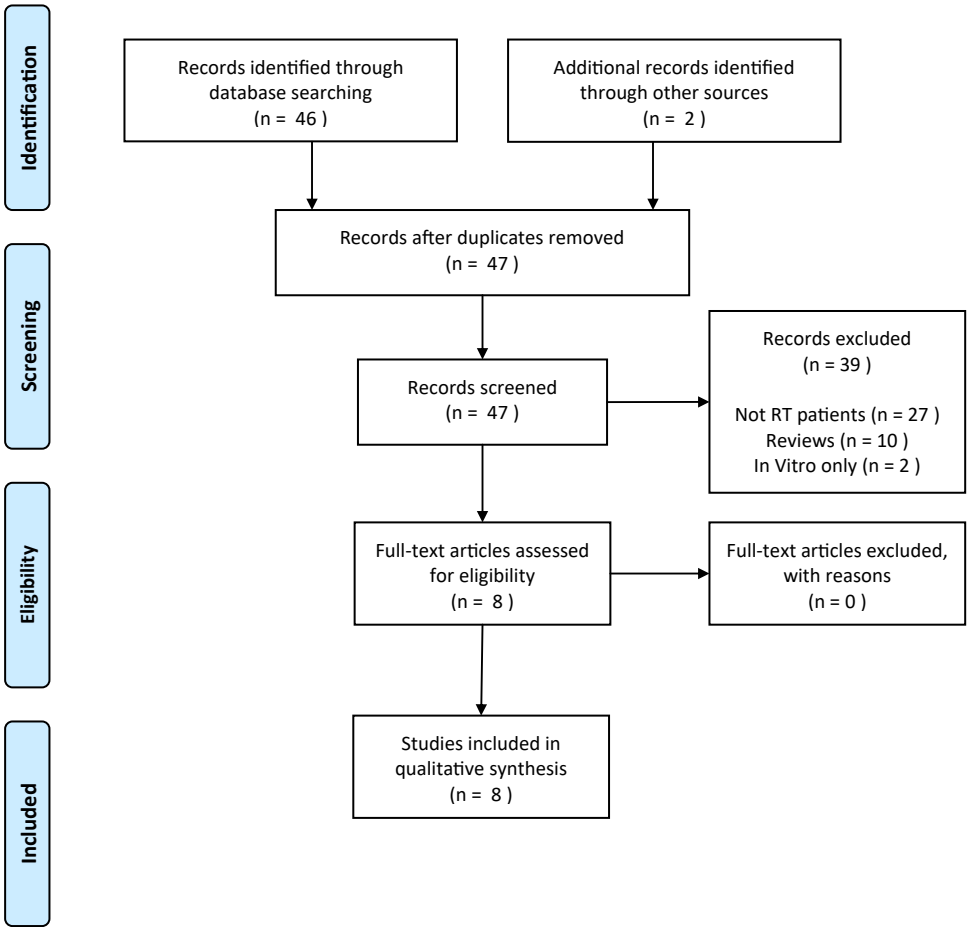

Figure 1. Prisma flow diagram.

tetrahydrocannabinol (1THC) versus placebo in a crossover study of 12 patients with inoperable lung cancer. When taking 1THC, patients reported "feeling better," freedom from pain, improved ability to fall asleep, and better quality of sleep. The investigators reported minimal side effects from 1THC. There was some mild drowsiness, 1 patient experienced tachycardia and feelings of disembodiment at first use (none thereafter), some mild confusion, and a reduction in feelings of vigor and elation. There was no change in feelings of anxiety or depression compared with the placebo, but marked increases in feelings of passivity and relaxation were seen with 1THC. The investigators felt that the safety and efficacy of 1THC to "calm" anxious patients warranted further comparisons to other sedatives and in other stressful clinical situations. The findings from this study should be interpreted in context with the risk of bias from the methodological choices. It is at a high risk of overall bias because the patients and medical staff were able to distinguish between THC and placebo because they recognized the psychoactive effects of 1THC. This lack of effective blinding, in combination with subjective outcome measures, may have influenced the findings. In addition, lack of control or reporting about the use of other sedatives may have obscured or enhanced the effect of 1THC.

Four studies from the 1980s have evaluated the effect of cannabinoids as an antiemetic during RT. Lucraft et al [17] compared the efficacy of 0.5 or 0.75 mg levonantradol (synthetic 9THC) versus 25 mg chlorpromazine (standard treatment at the time) to control RT-induced vomiting. Forty-three patients, who received a single fraction of palliative RT to the upper abdomen, were randomized to receive either 9THC or chlorpromazine if they began vomiting. 9THC was well tolerated (mild drowsiness and dry mouth), with 2 patients experiencing mild confusion and disorientation for a few hours after administration. The frequency of vomiting within 4 hours of RT was similar between the drugs (~56%), suggesting neither drug was particularly effective at controlling RT-induced vomiting. The authors postulated that higher doses of 9THC may be needed, but this may well increase the side effect profile. Although there is no information about whether the outcome evaluators were blinded to which drug the patients received when performing the qualitative evaluations, this study would seem to have a low risk of bias.

Ungerleider et al [18] compared the efficacy of prophylactic 7.5, 10, or 12.5 mg of synthetic 9THC (unreported brand) with 10 mg prochlorperazine (q 4 hrs) in 11 patients using a randomized crossover design. Radical intent RT was

Table 1
Summary of Articles Evaluating the Impact of Cannabinoids on Patients Receiving Radiation Therapy

Article	Intent	Pt Group	Analyzable Sample	Design	RT	Cannabinoid Type	Cannabinoid	Comparator	Timing of Intervention	Measures
Davies et al, 1974 [16]	Reduce anxiety	Lung, anxious	12	Crossover	Palliative, chest	Synthetic	10 mg 1THC	Placebo	Before RT	Qual Likert scale Pt reports
	Outcome: 1THC caused drowsiness and improved sleep, reduced pain, marked increases in relaxation Cannabinoid S/E: Increased fatigue and confusion, reduced elation and vigor; slight tachycardia and hypotension									
Lucraft et al, 1982 [17]	Prevent vomiting	Any	43	RCT	Palliative, upper abdomen	Synthetic	0.5 or 0.75 mg 9THC	25 mg Chlorpromazine	During RT	Qual Interviews Pt reports
	Outcome: Frequency of vomiting within 4 h of RT was similar between the drugs (~56%) Cannabinoid S/E: Mild, transient drowsiness and dry mouth									
Ungerleider et al, 1984 [18]	Prevent nausea & vomiting	Pelvis or abdomen cancers	7	Cross-over	Radical, abdomen or pelvis	Synthetic	7.5, 10 or 12.5 mg 9THC	10 mg Prochlorperazine (q 4 h)	During RT	Quant Likert scale Pt reports
	Outcome: 9THC reduced vomiting (0.43 vs. 1.0; ns), improved ability to maintain appetite (1.8 vs. 1.5; $P < .05$), improved concentration (+0.4 vs. −0.4; $P < .05$) Cannabinoid S/E: Mild dizziness, dry mouth, tachycardia, and space-time distortion (2 patients withdrawn because of intolerable dizziness and depersonalization)									
Priestman et al, 1984 [19]	Control nausea & vomiting	Abdomen cancers, Metoclopramide ineffective	6	Cohort	Radical, abdomen	Synthetic	1mg bd 9THC	10 mg tds Metoclopramide	During RT	Qual Pt diary
	Outcome: 9THC effectively reduced nausea and vomiting in 100% of patients not adequately controlled by standard therapy (50%) Cannabinoid S/E: Moderate dry mouth, mild lightheadedness and dizziness, mild drowsiness									
Priestman et al, 1987 [20]	Control nausea & vomiting	Abdomen cancers	40	Cross-over	Radical, abdomen	Synthetic	1mg bd 9THC	10 mg tds Metoclopramide	During RT	Qual Pt diary
	Outcome: Early in treatment, Metoclopramide was more effective at reducing vomiting, but by day 6, 9THC was more effective (0.11 vs. 0.17; $P < .04$) Cannabinoid S/E: Dizziness (30%), fatigue (25%), disorientation (20%), dry mouth (15%)									
Guzman et al, 2006 [21]	Reduce tumor progression	Recurrent glioblastoma	9	Observational	Palliative, brain	Synthetic	intratumoral 9THC	None	After RT	Quant Physician reports
	Outcome: THC did not stabilize tumor volume, survival was not improved. Marked reductions in headache, hallucinations, motor deficits, dysphasia, and cranial hypertension Cannabinoid S/E: Transient episodes of mild euphoria were seen in 2 patients									
Cote et al, 2016 [22]	Improve QoL & reduce RT S/E	H&N	56	RCT	Radical, H&N	Synthetic	0.5–2 mg 9THC	Placebo	During RT	Quant Validated Q
	Outcome: No significant difference in QoL between the 9THC and placebo. Pain, appetite, weight, nausea, and quality of sleep were not improved by 9THC. Cannabinoid S/E: 9THC was well tolerated, did not increase drowsiness, anxiety, or xerostomia.									
Elliot et al, 2016 [23]	Improve QoL & reduce RT S/E	H&N	15	Observational	Radical, H&N	Phytocannabinoids	Daily smoking	None	After RT	Quant Validated Q
	Outcome: Phytocannabinoids had no effect on QoL. Participants reported symptom relief for pain (67%), appetite (60%), xerostomia (53%), sticky saliva (47%), difficulty chewing (33%), dysphagia (60%), muscle spasm (47%), weight gain/stability (73%), depression (67%), and anxiety (33%). Cannabinoid S/E: Not reported									

H&N, head and neck; ITHC, Δ1-trans-tetrahydrocannabinol; Q, questionnaires; QoL, quality of life; Qual, qualitative metrics; Quant, quantitative metrics; RCT, randomized controlled trial; RT, radiation therapy; S/E, side effects; 9THC, Δ9-trans-tetrahydrocannabinol.

Table 2
Risk of Bias Analysis of the 8 Studies, Using RoB 2.0 (Randomized Trials) and ROBINS-I (Nonrandomized Trials) Critical Review Frameworks

Domains (Risk of Bias From…)							
RoB 2.0	Randomization			Plan Deviation	Missing Data	Measurement	Reporting
Davies, 1974 [16]	LOW			SOME CONCERNS	LOW	HIGH	LOW
Lucraft, 1982 [17]	LOW			LOW	LOW	LOW	LOW
Ungerleider, 1984 [18]	LOW			HIGH	LOW	HIGH	LOW
Priestman, 1987 [20]	LOW			HIGH	LOW	LOW	HIGH
Cote, 2016 [22]	LOW			LOW	LOW	LOW	LOW
ROBINS-I	Confounding	Participant Selection	Intervention Defined				
Priestman, 1984 [19]	LOW	CRITICAL	LOW	LOW	LOW	MODERATE	LOW
Guzman, 2006 [21]	SERIOUS	LOW	LOW	LOW	LOW	SERIOUS	LOW
Elliott, 2016 [23]	CRITICAL	CRITICAL	LOW	LOW	LOW	SERIOUS	LOW

delivered to the abdomen or pelvis. Of the 11 patients entered into the study, 4 were withdrawn because of excessive nausea and vomiting (1 patient – drug not reported), intolerable dizziness and depersonalization from 9THC (2 patients), and discontinued RT (1 patient). Although the small number of remaining patients (7 patients) makes the statistics difficult to interpret, patient ratings of reduced vomiting (0.43 vs. 1.0; ns) and improved appetite (1.8 vs. 1.5; $P < .05$) favored 9THC. No meaningful impact on nausea was seen with 9THC. For those who remained in the study, side effects from 9THC were mild and not considered problematic. The authors concluded that 9THC was slightly more efficacious than prochlorperazine, with minimal side effects. This study is, however, at high risk of bias. Despite the double-blind design, participants were likely aware of the assigned intervention as "5 of 6 patients had previous experience with marijuana (cannabis)" and would recognize when they were taking it based on its psychoactive effects. This, combined with the subjective outcome measures, may have influenced the findings. In addition, 2 of the 11 participants were withdrawn from the study owing to intolerable THC side effects, but these were not considered when the authors concluded that THC side effects were "mild."

Priestman & Priestman [19] used 1 mg bd nabilone (synthetic 9THC) to control nausea and vomiting in 6 patients with abdominal RT in whom 10 mg tds metoclopramide was ineffective. 9THC was effective at controlling nausea and vomiting for all 6 patients for the remainder of their RT course. Moderate side effects such as dry mouth (3 patients) and light-headedness (2 patients) were seen with 9THC. The authors concluded that 9THC is useful in patients with multifraction RT with nausea and vomiting not adequately controlled by metoclopramide. The findings from this research have a high risk of bias because of lack of randomization and lack of outcome assessor blinding. So, the study team went on to perform a randomized clinical trial [24], where they compared the efficacy of 1 mg bd nabilone with 10 mg tds metoclopramide in 40 patients experiencing RT-induced nausea using a double-blind, crossover design. Early in treatment, metoclopramide was more effective at reducing vomiting, but by day 6, 9THC was significantly more effective (0.11 vs. 0.17; $P < .04$). There were no differences in the patient assessments of drug efficacy, but there were more side effects reported when using 9THC (50% vs. 20% with moderate/severe side effects; $P < .01$). The authors conclude that 9THC should only be used when metoclopramide is not effective or is contraindicated. The study findings were at high risk of bias as 18% of the cohort had unplanned crossovers between the interventions owing to lack of efficacy or toxicity that were not adjusted for in the analysis. In addition, there were multiple statistical tests looking for significant differences between the groups at various time points, with the potential to cause false positive results.

One study evaluated the effect of cannabinoids on survival and symptoms of progression after brain cancer recurrence after surgery and RT [25]. Guzman et al (2006) [21] administered an intratumoral infusion of synthetic 9THC (80–180 μg administered daily over a cycle of 10 days) in 9 patients. Median survival was 24 weeks after drug administration, and 2 patients survived for approximately 1 year. These findings are similar to those evaluating the efficacy of temozolomide (standard of care) [26]. Although tumor volumes did not stabilize and survival was not improved, marked reductions in the symptoms of progression (cephalalgia, hallucinations, motor deficits, dysphasia, cranial hypertension) were seen with 9THC. Transient episodes of mild euphoria were seen in 2 patients, but no other side effects of 9THC were noted. Based on these findings, and the tumor cell culture data included in this article, the authors suggest that additional studies should be performed to evaluate the tumor antiproliferative properties of 9THC. This small preliminary study is at high risk of bias as there were multiple variables that could have influenced the symptoms of progression (eg, use of corticosteroids) but were not controlled for. In addition, the assessment of the symptoms of progression was subjective and ad hoc.

In 2016, two studies evaluated the use of cannabinoids to mitigate RT side effects and improve quality of life (QoL) of patients with head and neck (H&N) cancer during and after RT. Côté et al [22] randomized 56 patients with H&N cancer to receive either 0.5 to 2 mg nabilone (synthetic 9THC) or placebo and evaluated the effect on QoL and side effects

during and 4 weeks after RT using validated questionnaires. There was no significant difference in QoL between the 9THC and placebo groups. The severity or duration of pain, appetite and weight stabilization, nausea, and quality of sleep or mood were not affected by 9THC. 9THC was well tolerated. This study appears to be at low risk of bias, and the authors concluded that the low dose of 9THC was not enough to improve QoL of patients with H&N cancer.

In the only study to evaluate the use of botanical cannabis in patients undergoing RT, Elliott et al [23] evaluated the use of medical "marijuana" in 15 patients with H&N cancer who had received RT or chemo-RT (approximately 45 months previously), using cross-sectional H&N QoL and symptom questionnaires. The study team did not administer cannabis; instead, cannabis use by the patients was an eligibility requirement. Although determining cannabinoid dose was impossible owing to the use of unknown THC/CBD composition and strength of cannabis, most patients reported smoking cannabis at least daily (80%). QoL results were similar to those of other studies of post-RT patients with H&N cancer [27]. The participants attributed symptom relief from cannabis for weight gain/stabilization (73%), depression (67%), pain (67%), appetite (60%), dysphagia (60%), xerostomia (53%), sticky saliva (47%), and muscle spasms (47%). No cannabinoid-related side effects were collected. These findings suggest that patients felt the use of botanical cannabis helped to minimize many side effects from chemo-RT 3 to 4 years after their treatment. However, several aspects of the study design make it at high risk of bias. First, the inclusion criteria that required patients to be taking cannabis may have resulted in bias, as the experiences of patients who had tried cannabis, but discontinued because of lack of effect, would not be represented. Second, other factors that may have influenced the study outcomes (ie, use of pain medication) were not collected.

Discussion

More than 20% of Canadian patients with cancer have used cannabis in the last 6 months [5]. The addition of cannabinoid therapies to RT clinical practice may carry the potential for improved healthcare outcomes for patients [3]. Unfortunately, most oncology professionals are ill-prepared to support these patients [10,28,29]. The purpose of this scoping review was to address this knowledge gap, by summarizing the literature on the benefits and harms of cannabis use before, during, or after RT.

After a thorough literature search, only 8 studies that evaluated the impact of THC on patients undergoing RT were found. The use of cannabinoids was reported to calm anxious patients about to start RT, reduce nausea and vomiting consistent with the contemporary standard of care, reduce the symptoms of relapse for patients with glioma, and provide symptom relief >3 years after H&N chemo-RT. Unfortunately, most of these studies have significant design flaws that carry a high risk of bias. All contain very small numbers of patients that may lack the statistical power to detect significant differences between the groups. There are consistent challenges related to effective blinding for both patients and study staff, owing to the obvious psychoactive effects of THC. Differences in dosing, outcome measures, and

Table 3
Active and Planned Cannabis and Cannabinoid Studies in Patients Receiving RT

Title	Country	Status	Design	Cannabinoid Type	Radiation	Outcome Measures
Cannabis oil and radiation therapy for the management of pain	Canada	Not yet recruiting	Randomized, double-blind, placebo-controlled	Capsule Botanical extract 1:1 THC/CBD	Palliative RT to the symptomatic site	• Pain intensity • QoL
Medical cannabis during chemoradiation for head and neck cancer	US	Recruiting	Single prospective cohort	Ingestion method not noted Low THC: low CBD Low THC: high CBD high THC: low CBD high THC: high CBD	Definitive RT to head and neck region, concurrent with chemo	• Adherence to procuring cannabis
Tolerability of cannabis in patients receiving concurrent chemoradiation for glioblastoma	US	Recruiting	Single arm feasibility study	Smoked Botanical CBD 4.8%: THC 3.23%	Brain RT 60 Gy in 30f with temozolomide	• Cannabis-related adverse events
Investigation of cannabis for pain and inflammation in lung cancer	US	Withdrawn (2019, funding)	Randomized double-blind, placebo-controlled study	Smoked or Vaped Botanical 15.76% CBD; 3.11% THC	Undergoing RT for lung cancer	• Pain • Sickness impact • QoL • Mood & appetite • PET for esophagitis
Study of single doses of sativex in treatment-induced mucositis	UK	Terminated (2015, Slow recruitment)	Single cohort	Spray Synthetic 1:1 THC/CBD	Definitive RT to head and neck region, concurrent with chemo	• Pharmacokinetics • Cannabis-related adverse events

CBD, cannabidiol; QoL, quality of life; THC, tetrahydrocannabinol; RT, radiation therapy.
From www.clinicaltrials.com, Accessed May 21, 2019.

inclusion criteria make comparisons between the studies difficult, even when the primary outcomes are similar (ie, nausea and vomiting). Finally, all but one of these studies used synthetic THC rather than whole plant phytocannabinoids. It is now believed that whole plant phytocannabinoids possess the synergistic contributions of THC, CBD, and terpenoids that increase the effectiveness and mitigate the side effects of THC and interact with different endocannabinoid receptors [1]. For example CBD has an affinity for cannabinoid receptors in the gastrointestinal tract, and may therefore have a greater effect on nausea than 9THC [30], without the accompanying euphoric side effects [31]. Modern study approaches now include various ratios of THC to CBD from botanical sources to determine the effect of these factors.

Based on the weak evidence noted previously, it is not yet known whether taking cannabis before, during, or after RT will influence patient outcomes. All of these studies went on to recommend further research on the use of cannabinoids by patients undergoing RT, and studies that resolve the methodological limitations of previous evaluations are immediately needed. Unfortunately, there are currently no active studies evaluating the use of cannabis and RT in Canada (Table 3). One Canadian trial is registered with www.clinicaltrials.gov but is not yet recruiting. Two US studies are actively recruiting to determine cannabinoid use adherence and botanical cannabis side effects, and two studies have been terminated.

Although the aforementioned studies evaluated the use of cannabinoids to mitigate anxiety, nausea, symptoms of brain tumor progression, and H&N QoL in patients undergoing RT, patients with cancer also frequently report using cannabis to improve pain, appetite, and sleep [5,7,11,27,32]. In a systematic review of the health effects of cannabinoids [33], the US National Academies of Sciences, Engineering, and Medicine evaluated >10,000 studies and determined that there is substantial evidence that cannabinoids are an effective treatment for chronic pain. There is moderate evidence that cannabinoids are effective for improving short-term sleep outcomes and several articles published after the National Academies review indicate that there is now moderate evidence of the effectiveness of cannabinoids to increase appetite for patients with cancer [34,35].

For those studies that reported the side effects of oral cannabinoids, all but one reported only mild episodes of drowsiness, dry mouth, tachycardia, and hypotension with ≤2 mg synthetic 9THC. Only Priestman et al (1987) [20] saw substantial rates of dizziness, fatigue, and disorientation with 2 mg of 9THC, perhaps because of a larger sample size. These rates of side effects were similar to those reported by Ungerleider et al [18] who administered between 7.5 and 12.5 mg of 9THC and Davies et al [16] who administered 10 mg of 1THC. Despite the use of inconsistent and highly subjective side effect reporting, it would seem that ≤2 mg of 9THC resulted in minimal side effects in the population of patients undergoing RT. A meta-analysis of 321 trials (total of 8,168 patients) of the use of medical cannabinoids categorized the most common side events as mild dizziness (13.6%), mild drowsiness (12.5%), and dry mouth (7.9%) [36]. Other side effects found in the RT studies, such as tachycardia, hypotension, disorientation, and confusion were reported in <1.7% of patients [36]. It is also important to note that these short, cross-sectional RT studies were not able to measure the impact of long-term cannabis consumption, which includes a 9% incidence of developing a use disorder [37].

This scoping review has some strengths and limitations. The age of many of the studies under review resulted in the published article being the only source material for the risk of bias assessment. It is possible therefore that relying solely on the published article may under or over estimate the risk of bias because of the lack of detailed methodological information [38]. Both the ROBINS-I and RoB tools focus on a study's internal validity; this is distinct from issues of generalizability, where outcomes may not be applicable to groups of individuals not included in the studies [14,15]. It is acknowledged that the number of studies included in this review is very low and the risk of bias for most studies is high. This makes it difficult to draw meaningful conclusions from the available literature, but this scoping review is the first to describe the use of cannabinoids in patients before, during, or after radiation therapy.

Conclusions

There is very little known about the interaction of RT and cannabinoids. There is limited evidence that the use of THC may calm anxious patients undergoing RT, reduce RT nausea and vomiting, reduce the symptoms of relapse after RT for patients with glioma, and provide symptom relief after H&N RT. However, the majority of these studies had significant design flaws, poor statistical power, and evaluated only synthetic THC. Well-designed randomized controlled trials that evaluate the efficacy of botanical cannabinoids are urgently needed so patients with cancer who are deciding whether to take cannabinoids during RT can be adequately supported.

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