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REVIEW

MASCC guideline: cannabis for cancer-related pain and risk of harms and adverse events

Josephine To[1] · Mellar Davis[2] · Andrea Sbrana[3] · Bryony Alderman[4] · David Hui[5] · Sandip Mukhopadhyay[6] · Carole Bouleuc[7] · Amy A. Case[8,9] · Koji Amano[10] · Gregory B. Crawford[11] · Giulia de Feo[12] · Kimberson Tanco[5] · Jessica Garsed[13]

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Abstract

Background Approximately 18% of patients with cancer use cannabis at one time as palliation or treatment for their cancer. We performed a systematic review of randomized cannabis cancer trials to establish a guideline for its use in pain and to summarize the risk of harm and adverse events when used for any indication in cancer patients.

Methods A systematic review of randomized trials with or without meta-analysis was carried out from MEDLINE, CCTR, Embase, and PsychINFO. The search involved randomized trials of cannabis in cancer patients. The search ended on November 12, 2021. The Jadad grading system was used for grading quality. Inclusion criteria for articles were randomized trials or systematic reviews of randomized trials of cannabinoids versus either placebo or active comparator explicitly in adult patients with cancer.

Results Thirty-four systematic reviews and randomized trials met the eligibility criteria for cancer pain. Seven were randomized trials involving patients with cancer pain. Two trials had positive primary endpoints, which could not be reproduced in similarly designed trials. High-quality systematic reviews with meta-analyses found little evidence that cannabinoids are an effective adjuvant or analgesic to cancer pain. Seven systematic reviews and randomized trials related to harms and adverse events were included. There was inconsistent evidence about the types and levels of harm patients may experience when using cannabinoids.

Conclusion The MASCC panel recommends against the use of cannabinoids as an adjuvant analgesic for cancer pain and suggests that the potential risk of harm and adverse events be carefully considered for all cancer patients, particularly with treatment with a checkpoint inhibitor.

Keywords Adverse events · Cannabinoids · Cancer

✉ Mellar Davis
mdavis2@geisinger.edu

[1] Division of Aged Care, Rehabilitation and Palliative Care, Northern Adelaide Local Health Network, Adelaide, Australia

[2] Palliative Care Department, Geisinger Medical System, Danville, USA

[3] University of Pisa, Pisa, Italy

[4] Frimley Park Hospital, Frimley, UK

[5] Department of Palliative Care, Rehabilitation and Integrative Medicine, University of Texas MD Anderson Cancer Center, Houston, TX, USA

[6] Indian Council of Medical Research, New Delhi, India

[7] Department of Supportive and Palliative Care, P.S.L. University, Institut Curie, Paris, France

[8] Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

[9] Division of Geriatrics and Palliative Medicine, University at Buffalo Jacobs School of Medicine and Biomedical Sciences, Buffalo, USA

[10] Department of Palliative Medicine, National Cancer Center Hospital, Tokyo, Japan

[11] Northern Adelaide Local Health Network, South Australia, Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, Australia

[12] Instituto Nazionale dei Tumori, Milan, Italy

[13] Geisinger Medical Center, Danville, USA

Introduction

Cannabinoids have become a popular complementary symptom treatment option for patients with cancer. Prominent among these symptoms is cancer pain [1–6]. It is estimated that 18% of patients use cannabis at one time or another during the treatment as cancer treatment or as palliation [7]. The most common symptom for which patients take medical cannabis is pain and less so for non-pain symptoms such as sleeping disorders, nausea, loss of appetite, and anxiety [6, 8, 9]. As dispensaries increase in the USA and more states allow cannabis to be used for recreational purposes, cannabis use by patients with cancer is likely to increase. The liberal use of cannabis may be an international trend and not limited to the USA [10]. The ongoing opioid epidemic and fear of opioids may have encouraged states, specific organizations, and individuals to use cannabis for moderate to severe cancer pain rather than opioids or as an adjuvant to opioid therapy [11–13]. Retrospective studies have reported significantly improved symptom responses, including pain with cannabinoids [13].

Randomized trials of cannabinoids are essential to gauge the benefits or lack of benefits of cannabinoids in managing symptoms in patients with cancer. Cannabinoids have been mainly used as an adjunct analgesic in trials rather than as a primary analgesic [14–23]. It is essential to know how cannabinoids influence not only symptoms. It is also important to understand how cannabinoids may influence cancer biology. Little is known about the interactions between chemotherapy/or targeted therapy, immune therapy, and cannabinoids and how this may influence response and survival.

Malignant cells express cannabinoid receptors which may act as suppressors of tumor growth and metastases or may promote cancer growth and metastatic potential [24–29]. Immune therapy in the form of checkpoint inhibitors is increasingly essential in treating cancers. Cannabinoids are immunosuppressive and impair responses to checkpoint inhibitors [30, 31].

Very few guidelines have evidence to guide cannabinoid prescriptions during cancer therapy or during palliation in those with advanced cancer. The society of Gynecological Oncology Clinical Practice statement published in 2020 stated that "randomized studies of THC (tetrahydrocannabinol) and CBD (cannabidiol) combinations show improvement in pain scores albeit without opioid reduction" [32]. The European Pain Federation concluded that "cannabis-based medicines may be reasonably considered for chronic neuropathic pain. For all other chronic pain conditions (cancer, non-neuropathic pain), cannabis-based medicines should be considered an individual therapeutic trial" [33]. In contradistinction to the Gynecological Oncology Clinical Practice statement, the International Association for the Study of Pain (IASP) does not currently endorse the use of Cannabis or cannabinoids for pain relief due to the lack of evidence [34].

While there is a large amount of literature about the potential harms and adverse events of cannabis, the diversity of products and combinations used makes it difficult to compare reports. Furthermore, there needs to be more standardization of how this data is collected, e.g., what tools are used, self-report or patient interview, or when and over what period this data is collected. Harms and adverse events are usually included as secondary aims within a study, and a large amount is from non-randomized, non-controlled studies. These factors have meant little guidance about managing the risk of harm and adverse events in a clinical setting.

Part of the difficulty in interpreting trials is the "spin" within the manuscript. Spin is found in up to 55% of analgesic trials [35]. Spin is particularly prevalent in reports of studies with the non-significant primary outcome [36, 37]. Spin is the practice of reporting misleading conclusions suggesting favorable results. Spin interpretations are more favorably presented in written manuscripts than the actual results. Spin practices, for example, may use words like "trends" for non-significant findings or emphasize secondary outcomes where the study's primary outcomes are not significant. Spin involves selective reporting of results or post hoc explorations of study data within the manuscript to promote a more favorable outcome [37, 38]. Spin is a "specific reporting strategy whatever the motive to highlight that the experimental treatment is beneficial despite a statistically nonsignificant difference of the primary outcome" for which the trial was powered. "It distracts the reader from statistically nonsignificant results" [38].

Multiple systematic reviews centered on cannabinoids and pain have been published and are reviewed in some detail further in this manuscript. The value of cannabinoids as an analgesic for cancer pain is controversial. As a result, we conducted a systematic review of randomized trials centered on the efficacy of cannabinoids for cancer-associated pain in particular. We sought to balance the evidence of cannabinoids for cancer pain against the potential harms to establish an evidence-based guideline.

Methods

A systematic review of randomized trials and a review of systematic reviews and meta-analysis were carried out and are outlined in the Appendix. The search identified randomized trials of cannabinoids in patients with cancer from 1975 up to November 12, 2021. The literature search strategy

Table 1 MASCC levels of evidence

I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies; randomized trials with low false-positive and false-negative errors (high power)
II	Evidence obtained from at least one well-designed experimental study; randomized trials with high false-positive and/or false-negative errors (low power)
III	Evidence obtained from well-designed, quasi-experimental studies, such as non-randomized, controlled single-group, pretest-posttest comparison, cohort, time, or matched case-control series
IV	Evidence was obtained from well-designed, non-experimental studies, such as comparative and correlational descriptive and case studies
V	Evidence obtained from case reports and clinical examples

Table 2 MASCC grading of guidelines

A	Evidence of type I or consistent findings from multiple studies of type II, III, or IV
B	Evidence of types II, III, or IV and findings are generally consistent
C	Evidence of types II, III, or IV and findings are inconsistent
D	Little or no systematic empirical evidence

involved the MEDLINE, CCTR, Embase, and PsychINFO databases. The search results were reviewed separately for treatment of cancer pain and harms or adverse events. The pain outcomes of interest were improvement in analgesia measured by a standardized intensity scale (numerical scale 0–10, no pain to severe pain; a visual analog scale; or a categorical scale). Harms were those which were gastrointestinal or neuropsychiatric (lethargy, dizziness, fatigue, nausea and vomiting, diarrhea, and depression).

Inclusion criteria were as follows:

- Randomized controlled trials (RCT) or systematic reviews of randomized RCTs of cannabinoids versus either a placebo or an active comparator.
- Cancer patients over the age of 18 years.
- For harms and adverse events, systematic reviews were included if there was an explicit outcome (either primary or secondary) of the review.

Exclusion criteria were as follows:

- Publications not written in English
- Conference abstracts and other non-peer-reviewed publications
- Unavailability of full-text articles

The Jadad grading system was used for assessing the quality of reporting. This grading system considers blinding (up to 2 points), randomization (up to two points), and reporting of dropouts (up to one point), with higher scores reflecting better quality [39].

Studies were assessed for spin if the primary outcome of the randomized trial was not acheived. The panel reviewed the findings and a consensus was acheived after review.

The level of evidence is outlined in Table 1. Table 2 outlines the grade used for the guideline provided in Table 2 and the category of the guideline in Table 3. The consensus panel adopted the evidence, grade, and category level from MASCC. The panel met virtually several times in 2021 and 2022. The guideline committee of MASCC reviewed the guideline. Procedures for MASCC review and endorsement of an external guideline were followed. The MASCC Guidelines Committee makes a recommendation to the MASCC Executive Committee. The MASCC Executive Committee then makes the final decision, which the executive director communicates to the external organization requesting the endorsement. One of the authors extracted and reviewed data (M.P.D.), while two independently reviewed the data (J.T., AS), which was placed in a table. Spin was added based upon criteria published and added to the table [35]. A consensus about the presence of spin was achieved through virtual meetings and by review of Table 4.

Table 3 MASCC categories of guidelines

Recommendation	Reserved for guidelines that are based on level I or level II evidence
Suggestion	Used for guidelines that are based on level III, level IV, and level V evidence: this implies panel consensus on the interpretation of this evidence
No guideline possible	Used when there is insufficient evidence on which to base a guideline. This implies (1) that there is little or no evidence regarding the practice in question or (2) that the panel lacks consensus on the interpretation of existing evidence

Table 4 Randomized trial evidence for cannabis benefits in treating cancer pain

Author(s) (year)	Number/study design/time	Control	Cannabis intervention	Jadad rating	Outcomes	Results	Adverse effects	Spin
Pain								
Noyes, 1975	$N = 10$ crossover single dose, opioid tolerant	Placebo	THC 5, 10, 15, 20 mg	2	Primary-hourly pain intensity by categorical scale Secondary-pain relief by categorical scale, sum of pain intensity and relief	THC 5, 10 mg > placebo. Scores for combined low dose (5 mg or 10 mg) and high dose (15 or 20 mg) combined—"Pain relief superior to placebo at high dose levels"	20 mg very sedated, 15 mg drowsy, 2/10 euphoria at higher dose	No
Jochimsen, 1978	$N = 37$ crossover , single dose, opioid tolerant	Placebo	Benzopyranoperidine (BPP), 2 and 4 mg, codeine 60 and 120 mg	4	VAS (0–100 mm) hourly, 11-item symptom scale for psychic effects	BPP = placebo, codeine > placebo	2 dropouts, BPP = codeine	No
Johnson, 2010 (GW Pharma Inc funded the primary author)	$N = 177$, parallel, opioid tolerant with MEDD 80-100, 2 weeks	Placebo	Nabiximol oral spray (2.7 mg THC/2.5 mg CBD), THC oral spray, self-titrated week 1	4	Co-primary endpoints—BTP and NRS (either < 0.025, both < 0.05) Secondary—sleep, nausea, memory, appetite, BPI-SF, EORTC-QLQ-C30, mean daily dose breakthrough medication	BTP-NS THC/CBD $p = 0.024$—median THC-NS, not opioid sparing	Worse memory with THC/CBD and THC, appetite worse with THC/CBD and THC, worse nausea with THC/CBD	Use of "trend toward improvement" in QLQ-C30 with a $p = 0.11$, "trend toward improvement" constipation $p = 0.23$

Table 4 (continued)

Author(s) (year)	Number/study design/time	Control	Cannabis intervention	Jadad rating	Outcomes	Results	Adverse effects	Spin
Portenoy 2012 (both GW Pharma and Otsuka funded,2 co-authors were pharma employed)	$N = 360$, parallel, opioid tolerant, 5 weeks	Placebo	Nabiximol 1–4 sprays, 6–10 sprays, 11–16 sprays	5	Primary—30% reduction in pain intensity by NRS, last 3 days Secondary—BPI-SF, EORTC-QLQ-C30, PAC-QOL, MADRS, PGIC	263 completed. No difference NRS $p = 0.84$, responder analysis $p = 0.59$, improved response in low dose, improved sleep-in low-dose group. No difference in PAC-QOL, MADRS, EORTC-QLQ-C30, BPI-SF	Discontinuation greater in the high dose, deaths were highest in the low-dose group, most deaths from disease progression	Post hoc exploration of lower doses. "Some overall treatment effect $p = 0.072$." Comparison of individual arms rather than cross comparison, emphasis on secondary outcomes, "3 nabiximols group showed better response than placebo in opioid use-approached statistical significance $p = 0.077$"; "no significant difference in response in 30% responder rate analysis, but treatment effect in favor of combined nabiximols groups when comparing proportion of responders across the full range of response"
Lynch 2014 (GW Pharma supplied the drug but no funding from the company)	$N = 18$, 2 on opioids, parallel, 5 weeks, chemotherapy neuropathy > 3 months	Placebo	Nabiximol up to 12 sprays	4	Primary-NRS Secondary—SF-36, quantitative sensory testing	No difference in between-group comparison $p = 0.52$	2 dropouts, fatigue, dizziness, dry mouth, and nausea	Post hoc responders' analysis; "five participants had a 2-point decrease in NRS," between-subject comparison $p = 0.34$, use of within-group changes to calculate N.N.T

Table 4 (continued)

Author(s) (year)	Number/study design/time	Control	Cannabis intervention	Jadad rating	Outcomes	Results	Adverse effects	Spin
Cote 2016 (Valeant Pharmaceuticals provide nabilone)	$N = 56$, parallel, 7 weeks, HN cancer treated with surgery, radiation or ,chemotherapy with radiation	Placebo	Nabilone titrated up to 1mg bid	5	15-point improvement in EORTC-QLQ-C30 NH35 Secondary—VAS for pain intensity, analgesic use, weight, feeding tube dependence, appetite nausea	No difference in QOL. No difference in pain or analgesic use, no improvement in appetite, weight, nausea, sleep, or mood	9 in nabilone dropped out, 15 in placebo	No
Fallon 2017 (funded by Otsuka Pharmaceuticals with co-authors employed by Otsuka and GW Pharmaceuticals)	2 studies Study 1—parallel Study2—enrichment enrolment randomized withdrawal (EERW), study 1 $N = 399$ Study 2 $N = 406$, both opioid tolerant, pain $\geq 4 \leq 8$ NRS, study 1 and 2–5 weeks	Placebo	Study 1 nabiximol up to 10 sprays/day Study 2—titration to 15% or greater improvement in NRS over 4 days then randomized withdrawal	3	Primary study 1—improvement in daily average NRS weeks 3 and 5, study 2—mean change in NRS from randomized withdrawal at weeks 3 and 5 Secondary outcomes, study 1 change of NRS from baseline, worst pain NRS score, sleep, BTP, and total opioid dose, SGIC, PSQ, PGIC, constipation NRS	No difference in medium change in NRS (7.2% nabiximol, 9.5% placebo, $p = 0.274$ Study 2—equal worsening of pain during randomized withdrawal, $p = 0.917$, average NRS in randomized withdrawal not different, sleep not different Study 1—SGIC and PDIC improved with nabiximol, study 2—no improvement in SGIC, PCIC, no change in opioid requirement	Treatment emerging side effects are the same. In study 2, neoplasm progression occurred in 29.1% of those maintained on nabiximol and 14.6% randomized to placebo withdrawal	In unplanned post hoc analysis, US patients responded, < 65 years but not the rest of the world. "Although Sativex did not impact opioid use in either study, although total daily opioid dose exhibited a treatment effect in favour of Sativex that trended towards significance ($p = 0.053$)." Abstract states that treatment effects favoured with Sativex in quality-of-life questionnaires which was only true for study 1

Table 4 (continued)

Author(s) (year)	Number/study design/time	Control	Cannabis intervention	Jadad rating	Outcomes	Results	Adverse effects	Spin
Lichtman 2018 (supported by Otsuka and co-authors were employees of Otsuka and GW Pharmaceuticals)	$N = 397$, parallel, opioid tolerant with a MEDD ≥ 90 and NRS ≤ 4 ≤ 8, 5 weeks	Placebo	Nabiximol up to 10 sprays/day	3	Primary—percentage improvement from baseline to end of treatment of average pain by NRS Secondary—change from baseline in average NRS, worst pain, sleep, BTP, opioid dose, SGIC, PSQ, PGIC, constipation NRS	ITT—mean percent difference 10.7% nabiximol, 4.5% placebo $p = 0.0854$ PP—15.5% vs. 6.3% $p = 0.0378$ Secondary—no difference in average or worst pain, improved sleep $p = 0.027$. No difference in opioid doses or responders	58 nabiximol and 48 placebo patients dropped out. Deaths in placebo and nabiximol were the same. Treatment emerging side effects 35.2% nabiximol, 20.7% placebo	Authors state that SGIC, PSQ and PGIC "trended" to improvement ($p = 0.0521$, $p = 0.0861$, $p = 0.0836$) Unplanned post hoc analysis of US vs. other countries, pain SGIC, PSQ, PGIC improved in US Abstract emphasizes PGIC, SGIC, and US participant and secondary outcomes
Harms and adverse events								
Duran 2010 (nil)	$N = 7$ Parallel, CINV > 24 hours after MEC (carboplatin, cisplatin, cyclophosphamide, doxorubicin, idarubicin, ifosfamide, irinotecan, mitoxantrone, epirubicin), 120 h (days 0–4)	Placebo ($N = 9$)	THC 2.7 mg/CBD 2.5 mg spray (Sativex®), up to 8 sprays within any 4-h period every 24 h until day 4	5	Patient diary for number of vomits VAS for severity of nausea before each dose Compliance and safety—daily telephone interviews AEs—patient diary and structure questionnaire with daily telephone interviews	6/7 tolerated dose titration (one discontinued due to anxiety, somnolence, visual hallucinations, and confusion) 6/7 (86%) developed at least one AE (not significant of placebo); one was severe (patient withdrew as above during titration) No other withdrawals are due to AE. 4/7 satisfied with the treatment		Tolerability: withdrawal during titration period due to adverse events

Table 4 (continued)

Author(s) (year)	Number/study design/time	Control	Cannabis intervention	Jadad rating	Outcomes	Results	Adverse effects	Spin
Schloss, 2021 (funded by FIT-Bioceuticals; do not seem to have any strong links to existing cannabis products on the market)	$N = 88$, parallel, double-blind, dual active arms (different ratios), recurrent or inoperable high-grade glioma (GBM or astrocytoma Aa3r), 12 weeks	Retrospective	1:1 (4.6 mg/mL THC:4.8 mg/mL CBD) or 4:1 (15 mg/mL THC:3.8 mg/mL CBD) 0.20 mL bedtime titrated to 5 mL in one dose	4 (consort diagram does not add up)	Primary FACT-Br Tolerability via participant diary Secondary Treatment-related toxicity, blood safety markers, dose-response, and tumor growth over 12 weeks	3 dose reductions due to side effects which resolved with dose reduction (2 in 1:1, 1 in 4:1) Compared to a retrospective control group, less dexamethasone, and craniotomies, lower stable and progressive disease, and higher reduction in reduction in tumor size. No statistical comment was provided	"When associations between liver enzymes and the use of anticancer therapy were tested, a statistically significant association between raised GGT and temozolomide ($n = 30$; $p = 0.028$) was identified. Also, a small number of participants ($n = 6$) had been prescribed bevacizumab, and a statistically significant association with elevated ALP and GGT was found in this group. Similarly, the analysis identified a statistically significant association between lomustine patients on lomustine ($n = 4$) and raised ALP ($p = 0.001$)"	The retrospective control group was only used to look at tumor size and disease progression, not possible to comment on tolerability and adverse effects. The control group was matched, but if collected from the same time as the active trial patients is not explicitly described. Tolerability is not defined. "The primary outcome of this trial was tolerability and both cannabis product ratios were found to be well tolerated." One patient switched arms during the study. Adverse effects over time not done as ITT and reported as "The number of total side effects identified decreased during the trial from 57% to 41% by week 12"

Table 4 (continued)

Author(s) (year)	Number/study design/time	Control	Cannabis intervention	Jadad rating	Outcomes	Results	Adverse effects	Spin
Twelves 2021 (3/8 authors from GW Research Ltd, parent company is GW Pharmaceuticals; GW funded fellowship of one additional author; sponsored by GW)	$N = 12$, randomized, double-blind, placebo-controlled, GBM with first progression after RT and CT with temzolamide,1 year or until trial withdrawal	Placebo ($N = 9$)	Nabiximols 1 spray/day titrated by 1 spray/day up to 12 sprays/day (30 mg CBD/32.4 mg THC)	4 (placebo blinding not described in detail)	Tolerability and safety indicated by frequency and severity of TEAEs	Only 1 nabiximols patient completed the trial. All patients included in safety analysis. More severe TEAEs and higher incidence of serious TEAEs ($N = 4$)		Does not describe how TEAEs were assessed and how frequently. Difficult to match results narrative with withdrawals listed in flow diagram. Narrative grouped active and placebo reasons together. Some withdrawals related to toxicity not counted as due to AE. Difficult to determine number of patients with disease progression

I.R.B. approval was unnecessary as this was a systematic review of publicly available data without patient identifiers.

Results

The systematic review yielded 145 articles from MEDLINE, 419 from Embase, 62 from PsychINFO, and 203 from CCTR. The included studies are summarized in Table 4.

Pain

Thirty-four systematic reviews and randomized trials met the eligibility criteria for cancer pain. Seven randomized trials involving patients with cancer pain with the primary objective were relief from pain included, and these RCTs are summarized below.

Randomized trials

The study of Noyes, a single-dose study of THC versus placebo in a small number of patients, found that low-dose THC (5–10 mg) produced equivalent analgesia to high doses (15–20 mg). The peak benefit occurred at 3 h. For low-dose and 5 h for high-dose THC, most patients were on methadone [16]. So how did this add to the review? It is really not clear.

One of the two primary endpoints was positive in the three-arm randomized trial published by Johnson and colleagues [20]. There is an improvement in the numerical rating scale (NRS) with nabiximol spray (2.7 mg THC and 2.5 mg CBD per spray). Patients were on opioids and were opioid tolerant. The duration of treatment with the cannabis derivative in the study was 2 weeks. Patients on fentanyl were not included in the study. The median daily morphine equivalents (MEDD) ranged between 80 and 120. All patients had baseline pain severity greater than four on an NRS (0 no pain, ten severe pain). Because of two primary endpoints, significance was placed at $p = 0.025$. The number of sprays per day did not differ between nabiximol and placebo and THC and nabiximol (8.75 to 9.61). Interestingly, in contrast to Dr. Noyes' study, THC was not different from placebo in pain response [16, 17]. The ACOVA change in NRS was − 1.37 for nabiximol, − 1.01 for THC, and −0.69 for placebo. The difference between nabiximol and placebo was significant ($p = 0.014$). Pain responders defined as those individuals with a 30% or more significant reduction in NRS were 43% for nabiximol, 23% for THC, and 21% for placebo. There was a significant difference between nabiximol and placebo only ($p = 0.006$). The second primary endpoint was breakthrough pain, and there was no difference between cannabinoids and placebo. There was no difference in opioid doses and no opioid-sparing effect. Memory and concentration were worse with nabiximol. Appetite improved only with placebo but decreased significantly on nabiximol. Nausea was worse with nabiximol, and there was no improvement in quality of life with cannabinoids [20].

Similar studies by Dr. Portenoy and colleagues, Dr. Fallon and colleagues, and Lichtman and colleagues did not reproduce the primary outcome observed by Dr. Johnson and colleagues (see Table 4) [15, 18, 19]. These trials were supported by the pharmaceutical industry, had pharmaceutical industry employees as authors, and had a significant spin involving secondary endpoints. The study by Dr. Lynch and colleagues involved patients with chemotherapy-induced neuropathy and failed to find nabiximol helpful but used intragroup changes in pain intensity to generate a number needed to treat analysis which is a spin [23]. None of the trials were long enough to determine the influence of cannabinoids on cancer response and survival. None of the trials demonstrated reductions in opioid doses with cannabinoids.

Systematic reviews

There are multiple systematic reviews, some redundant, so we will review particular ones that are apropos to developing a guideline. Harrison and colleagues reviewed seven studies, including 827 participants. Six of the seven randomized studies included a placebo. The relative risk for pain control was 1.03 (95% confidence intervals 0.59 to 2.06), which was not different from the placebo [40]. Chapman and colleagues found that though small studies using THC reported analgesic benefits with cannabinoids when added to standard opioids, more extensive trials of cannabinoids were largely negative [41]. Darkovska-Serafimovska and colleagues included only three studies: the studies reported by Dr. Johnson, the Johnson follow-up paper, and the trial reported by Dr. Portnoy's study [42, 43]. The review reported a favorable conclusion based upon the secondary outcome from the Johnson study, which is quoted in the abstract. They provided recommendations as a treatment for ten actuations of nabiximol but also stated that further studies are required to confirm this recommendation. This systematic review missed multiple extensive studies, and its favorable review may be due to the limited number of studies included. A review by Shin and colleagues included randomized and observational studies and hence was biased. The review by Chung and colleagues provided no search method or grade of study. Only a single sentence at the beginning of each paragraph mentioned the primary adverse endpoints of the Portenoy, Fallon, and Lichtman reported studies. At the same time, the great majority of the review discussed the

positive secondary endpoints [44, 45]. The review by Meng and colleagues provided no search method and selectively reported randomized trials, small trials, and observational studies. Most of the discussion was on secondary and post hoc reported outcomes in various studies. The conclusion was that the clinical efficacy of cannabinoids is limited, and studies are of low quality [46].

The systematic review by Dr. Aviram and Samuelly-Leichtag published in 2017 included only the studies of Noyes, Staquet, and Johnson. Using randomized effect modeling, the standard mean difference in pain was − 0.76 (Hedges *g*) (95% confidence interval − 1.06 to − 0.45). This review was minimal and did not include the Portenoy, Lynch, and Cote reported studies [47]. A systematic review by Rabgay et al. involved cannabinoids in multiple pain phenotypes. Twenty-eight studies involved non-cancer pain, and 5 with cancer pain. The authors stated that THC appears superior to nabiximol, mainly based on the single-dose Noyes study [48]. A second systematic review and meta-analysis of 25 randomized trials, most of which involved chronic non-cancer pain, suggested a benefit in reducing pain intensity. The Cohen *d* for cannabinoids was − 0.58 (95% confidence intervals − 0.7 for to − 0.43) with placebo at − 0.39 (95% confidence intervals − 0.53 to − 0 0.26 ($p < 0.05$). The smaller trials demonstrated a more significant effect. However, only a minority of studies involved patients with cancer [49]. Nugent and colleagues published an overview of cannabinoids for chronic pain in 2017. Their review involved 27 randomized and observational studies. They found low-quality evidence for cannabinoids as an adjuvant to neuropathic pain analgesics and insufficient evidence in other pain populations [50].

Two meta-analyses, one by Dr. Boland and colleagues and one by Dr. Hauser et al., have the highest quality of evidence and are particularly well done [14, 51]. Dr. Boland and colleagues did a meta-analysis of 5 randomized trials of cannabis-based medicine compared to placebo as an adjuvant to cancer pain. There were no differences between cannabinoids and placebo using the average NRS as the primary outcome measure, − 0.21 (95% confidence intervals − 0.48 to 0.00) ($p = 0.14$). If only significant phase III trials were analyzed, the mean NRS difference was − 0.02 (95% confidence intervals − 0.21 to 0.16).

The meta-analysis by Dr. Hauser and colleagues included only randomized trials involving patients with cancer and pain [14]. The requirement to be included in the meta-analysis was that studies had at least 20 participants; the pain was cancer-related and not related to chemotherapy-induced neuropathy. The outcomes were based upon the Initiative of Methods Measurements and Pain Assessment in Clinical Trials (IMMPACT). Primary efficacy was determined to be at least a 50% reduction in pain severity. Secondary points were a responder's analysis based on at least a 30% reduction in pain severity and patient global impression of change (PGIC). In the trial, which utilized enrichment enrollment, and randomized withdrawal design, a less than 30% loss of pain relief from baseline was the primary endpoint. Other secondary endpoints were changes in opioid MEDD and breakthrough pain. The number needed to treat (N.N.T.) was an outcome; an N.N.T. < 10 is clinically significant. Five studies were eligible, and four that involved 1333 participants had quantitative measures for a meta-analysis. All of the eligible studies had funding provided by pharmaceutical companies. For the primary outcome, 93 of 786 patients on cannabinoids had at least a 50% reduction in pain intensity. In comparison, 53 of 547 placebo-treated patients had the same response (11.8% versus 9.7%, a risk difference of 0.00 with a 95% confidence interval of − 0.03 to 0.04) ($p = 0.82$). There was no heterogeneity observed. Two studies analyzed PGIC as an outcome. Ninety-four of 347 cannabinoid patients had an improvement versus 75 of 363 placebo-treated patients (27.1% versus 20.7%) (relative difference 0.06 95% confidence interval 0.00 to − 0.13, N.N.T. of 16). There was no reduction in opioid use with cannabinoids ($p = 0.11$). Four studies assessed the outcome using pain relief of at least 30%. Of 786 patients treated with cannabinoids, 231 had a pain reduction of at least 30%, while 145 of 547 placebo-treated patients responded (29.4% versus 26.5%) (relative difference 0.03, 95% confidence interval of − 0.02 to 0.08) ($p = 0.27$). The standard mean difference in pain was − 0.11 (95% confidence interval − 0.25 to 0.02) ($p = 0.09$). The maintenance of opioid doses is reported in 3 studies. The standard mean difference was 0.08 (95% confidence intervals − 0.10 to 0.27) ($p = 0.38$). Breakthrough pain opioid doses involved three studies and 971 participants. The standard mean difference was − 0.12 (95% confidence interval − 0.25 to 0.01) ($p = 0.06$). In the study that involved an enrichment enrollment randomized withdrawal, the loss of therapeutic response was − 0.31 (95% confidence interval − 0.57 to − 0.04) ($p = 0.02$). The mean pain intensity was 0.12 (95% confidence interval − 0.18 to 0.42) ($p = 0.43$), and maintenance of opioid doses was − 4.17 (95% confidence interval − 8.76 to 0.04) ($p = 0.08$).

Guideline

There is no level I evidence supporting cannabinoids as an analgesic for cancer pain. However, there is one randomized trial with one of two primary endpoints which suggest the benefits of cannabinoids and three randomized trials using the same cannabis product with primary adverse endpoints. The inconsistent results negate level II evidence. High-quality systematic reviews do not suggest clinically meaningful benefits to using cannabinoids as an adjuvant to cancer pain. There is a concern with the amount of spin in manuscripts

reporting the results of randomized trials and the close association with the pharmaceutical industry. Randomized trials have minimal types of cannabinoids used in trials which further hampers any recommendations. Another primary concern is the lack of long-term safety data both from the point of view of side effects (including cannabis use disorder) also regarding the influence of cannabinoids on cancer biology and anticancer responses. The recent report on the adverse influence of cannabinoids on checkpoint inhibitor cancer responses and survival should be a note of caution.[21] The panel recommends, in light of the evidence against empiric cannabinoids as an adjuvant analgesic for cancer pain, that patients should be treated solely on well-designed, low-bias registered cannabinoid trials.

Harms

Randomized controlled trials

We reviewed cannabis trials and systematic reviews for adverse effects and harms. After a review of the literature research, three randomized trials met the eligibility criteria to be included in the present review. Two were randomized, placebo-controlled trials [52, 53], and the third used a retrospective control group [54]. This retrospective control group was only used to review tumor size and disease progression compared to the intervention and not to compare tolerability and adverse events. All studies were of moderate quality (Jadad 4 and 5).

Duran et al. [52] designed a randomized, placebo-control clinical trial that investigated the use of cannabis-based medicine, compared to a placebo, to treat chemotherapy-induced nausea and vomiting. Cannabinoids were added to standard antiemetic prophylaxis 120 h after chemotherapy administration. Doses were 2.7 mg of THC, and 2.5 mg of CBD or placebo was administered as an oromucosal spray (Sativex®) up to three times in 2 h after chemotherapy. Patients were encouraged to titrate their dose until day 4, with ≤ sprays limited to 4 h every 24 h. Patients completed a diary that registered the number of vomits and the severity of nausea by VAS before every dose of the study drug until 120 h after chemotherapy. Tolerability was the primary endpoint, registered as the number of withdrawals from the study during the titration period due to adverse events. Sixteen patients, 7 in the experimental and 9 in the control arm, were in the study. One patient in the experimental arm withdrew from the study, whereas no withdrawals were observed in the control arm. There was no significant difference in the number of adverse events reported in the intervention group compared to the placebo (86% vs. 67%). Two or more patients in the intervention group reported somnolence, dry mouth, dizziness, anxiety, and confusion.

Schloss et al. [54] performed a phase II, double-blind, randomized clinical trial assessing two oral different cannabinoid ratios in 88 patients with recurrent or inoperable high-grade gliomas. Patients were randomized to receive a 1:1 and 4:1 ratio of THC:CBD (1:1 THC 4.6 mg/mL:CBD 4.8 mg/mL and 4:1 THC 15 mg/mL:CBD 3.8 mg/mL). The primary endpoint was assessing side effects according to Functional Assessment of Cancer Therapy-Brain (FACT-Br) from baseline to 12 weeks of therapy and the contemporary assessment through a patient's diary. Treatment-related toxicity was a secondary outcome. The 1:1 ratio resulted in being better tolerated in terms of physical ($p = 0.025$) and functional ($p = 0.014$) capacity and improved sleep ($p = 0.009$). 3.4% of participants had their dose reduced because of side effects, including shaking and night hallucinations. There was no evidence of tumor-inducing effects, noting that this was in comparison to the retrospective control group.

Twelves et al. [53] performed a phase 1, open-label, and phase 2, randomized, double-blind, placebo-controlled trial of nabiximols (6 patients in part 1, 12 patients in part 2) versus placebo (9 patients in part 2) in patients with recurrent glioblastoma. Safety was the primary endpoint of the trial. In part 1, three patients (50%) withdrew from the study because of grade 1 or 2 side effects, which included lethargy, dizziness, fatigue, nausea and vomiting, diarrhea, and depression. In part 2, 3 patients (41.2%) came off the study due to adverse events (1 for concentration impairment and urinary incontinence, two because of disease progression). It is important to note that this trial did not specify how adverse events were assessed nor how frequently. There was no evidence of tumor-inducing effects from the intervention measured by overall survival and comparison to EORTC-predicted median survival.

Systematic reviews

This review included five relevant systematic reviews: two in cancer pain [22, 51] and two in chemotherapy-induced nausea and vomiting [55, 56]. Articles were excluded if adverse events or harms were only included in the discussion.

Cancer pain

Five studies were included in these reviews [22, 51], four comparing nabiximols to placebo and one comparing THC:CBD, THC, and placebo.

There was no significant difference in reported adverse events, with dizziness, nausea, vomiting, somnolence, and fatigue most reported. Nervous system adverse events, including somnolence, were reported more frequently (OR 2.69 (1.54 to 4.71), $p < 0.001$) [51] and assessed to be

clinically relevant with an NNH of 10 [22]. There was a higher rate of study withdrawal due to adverse events, but this was not statistically significant.

Chemotherapy-induced nausea and vomiting

The Cochrane Review [56] included 23 RCTs; the cannabinoids studied were nabilone ($n = 12$) and dronabinol ($n = 11$). Compared to the placebo, there was a higher chance of withdrawal due to an adverse event and of "feeling high." Compared to prochlorperazine, there was an increased chance of dizziness, dysphoria, euphoria, "feeling high," and sedation. Withdrawal due to adverse events was higher in the cannabinoid arms. There were more minor effects compared to other antiemetics, which were insignificant.

Chow et al. [55] included seven studies (THC $n = 4$, nabilone $n = 2$, dronabinol $n = 1$). There was a significantly higher chance of dysphoria, euphoria, and sedation in the cannabinoid groups. No analysis of withdrawal due to adverse effects was performed.

Discussion

Pain

Patients participating in cannabinoid analgesic trials for cancer pain were uniformly opioid tolerant, and many were taking high doses (> 90 MEDD). Pharmaceutical companies with pharmaceutical employees supported the most extensive powered trials included as authors, which is worrisome for bias. The cannabinoids used were limited to nabiximols, with few trials using THC and nabilone. The quality of the studies was low to moderate on the Jadad scale, but there was a significant bias in reporting, particularly in the pharmaceutical industry–supported studies. The spin within the manuscripts may have diverted readers from the negative primary outcome and led them to believe that there were established benefits to cannabinoids as an effective adjuvant analgesic.

The adverse events of cannabinoids can be significant. There is a concern, mainly since there is limited long-term safety data for cannabinoids in cancer. Cannabis use disorder (CUD) is also a concern with long-term cannabinoid use; patients live longer with their cancer, and more survive their cancer. Promoting the use of cannabinoids has been propagated by potential "health benefits" and the absence of health concerns that are not well substantiated. CUD is defined by nine pathological patterns classified under impaired control, social impairment, risky behavior, physiological adaptation, and addiction risk of combining cannabinoids with opioids may be substantial, even if controversial [57]. A negative coping style is associated with cannabinoid abuse which can be amplified by living with cancer [58].

The enthusiasm for cannabinoids in cancer has been generated through observational and prospective cohort studies. The language of observational studies often implies a causal relationship between the use of cannabinoids and symptom response. Observational studies and prospective single-arm studies provide information about association but not about causation. The overinterpretation of associations in observational studies misleads many to accept the benefits of cannabinoids without randomized trial evidence [59]. The bias of pharmaceutical company–sponsored studies can be a concern [60, 61]. Replicability of studies is much more substantial evidence than a single positive randomized trial [62, 63]. What is evident in cannabinoid studies is that there is a lack of replicable results.

The belief that cannabinoids reduce opioid doses for cancer pain is not substantiated in randomized trials. Preclinical research supports the interactions between cannabinoids and opioid receptors [64, 65]. The drawback to combining these two compounds can be the accentuation of adverse opioid effects [66, 67]. The interactions between cannabinoids and opioids are pharmacodynamically and pharmacokinetically complex. For instance, cannabinoids influence buprenorphine bioavailability [68]. These complex interactions between opioids and cannabinoids are dose-related. In studies involving rhesus monkeys, THC did not enhance heroin use at low doses and attenuated heroin self-administration at high doses [69]. Subtherapeutic THC doses potentiated morphine analgesia and diminished morphine discrimination [70]. Opioids with higher intrinsic efficacies may have a better therapeutic coupling between cannabinoids and opioids. For instance, in rhesus monkeys, the combination of fentanyl and a CB1 agonist improved the dose-effect curve derived from experimental pain 53-fold; with morphine, it was 7.9-fold. On the other hand, a CB1 agonist did not improve analgesia when combined with nalbuphine, a kappa-opioid receptor agonist and mu receptor antagonist [71, 72]. Therefore, future trials need to control the opioid used in the study, the type of cannabinoids, and the dose of individual cannabinoids and opioids.

Harms

The systematic reviews showed some evidence of increased adverse events, including those leading to the withdrawal of cannabinoids. This finding in observational studies contrasts with the minor but often non-significant effects seen in the RCTs. It highlights the need for further studies to assess adverse events associated with cannabinoids carefully. In reviewing the studies where adverse events were a secondary aim, there is inconsistency in measuring and assessing adverse events. A well-designed study with standardized and preferably validated tools is required. The variability of cannabinoid products available and the variety of indications,

even within a cancer population, make results difficult to generalize. This product variability is a significant challenge for clinicians, mainly when use is unregulated. Patients may not disclose their cannabis use, making any assessment of potential harm impossible. Even if disclosed, with unregulated products, there is no guarantee of quality or consistency of constituents, potentially leading to a changing yet unquantifiable risk of harm. The included studies were in a minimal number of indications and patient cohorts, and it is unclear if the results can be generalized to all cancer patients in all indications. Even within a single cancer diagnosis, there are significant variations related to stage, type of treatment, and intent, which may influence the occurrence and perception of harm or adverse events.

Beyond the scope of this review, there is an increasing range of evidence about the potential harms of cannabinoids which are relevant in the cancer population. These harms are not detected in RCTs since these outcomes are observed at a population level and over time.

An association between cannabinoid use and decreased tumor responses to immunotherapy is reported, initially for nivolumab [73] and other checkpoint inhibitors [21]. These studies demonstrated either a decrease time to tumor progression, a reduced survival or both when patients were treated with cannabis and a checkpoint inhibitor.

A recent systematic review concluded that there is low-level evidence to suggest an association between cannabinoid use and the risk of developing testicular cancer [9]. An epidemiological study supports the genotoxicity of phytocannabinoids [74]; the proposed mechanism is epigenetic changes with cannabinoid exposure. These genetic changes are vertically transmitted across generations leading to increased congenital abnormalities [75] and the development of pediatric malignancies [76], including pediatric acute lymphoblastic leukemia [77]. These potential harms for future generations become more significant as cancer survivorship increases.

The evidence of drug interactions is of additional relevance in the cancer population. THC and CBD are substrates and inducers of some drug-metabolizing enzymes, including cytochrome P450s. Clinically significant interactions with antiepileptic medications are relevant for the cancer population because antiseizure medications are used for seizure management and as adjuvant analgesics. These interactions may also affect a range of other analgesics commonly used in cancer pain and palliative care [78]. Opioids and adjuvant analgesics such as amitriptyline require additional monitoring and dose modifications. Furthermore, THC is highly protein bound and may displace other protein-bound medicines. At the same time, patients with low albumin, which is quite common in advanced cancer, may be more sensitive to the effects of THC with more free drugs circulating. The specific details of concurrent medicines are rarely reported in studies, and the potential effect of any interactions cannot be determined.

More broadly, reviews have raised concerns about the cardiovascular adverse events of cannabinoids and increased rates of adverse events in older patients [79–81]. The well-known neuropsychiatric effects of cannabinoids, including anxiety and sedation, confound the assessment and management of confusion and somnolence associated with cancer, both common end-of-life symptoms. These effects from THC, in particular, can significantly affect driving safety, with it being an offense to drive under its influence in some jurisdictions [82]. Cannabis impairs driving ability which is compounded by the addition of other psychoactive medications. Including opioids. Hyperemesis with cannabinoids confounds the assessment and treatment of nausea and vomiting associated with cancer and its treatment. The balance of beneficial effects compared to potential adverse events needs to be considered in overall efficacy and improvement in quality of life.

The harms of cannabis should be discussed with patients who request cannabinoids. Where patients are already taking cannabinoids, disclosure of use should be encouraged, and patients should be monitored for potential adverse events. If any harms emerge, decisions around ongoing use should consider any actual or perceived benefits.

Best practices for managing patients on cannabinoids

Patients may be taking cannabinoids before referral for cancer treatment or palliative care or have elected to take cannabinoids after discussions of the pros and cons of cannabinoids. In this case, pharmacovigilance by the physician of record is essential. Patients should not be routinely advised to stop cannabinoids if they are already on cannabinoids. Physicians should document the dose (concentration) and frequency as well as the type of cannabinoids used by the patient. The goals/reasons for cannabinoid use, as described by the patient, should be documented and followed using standard symptom assessment tools. Standard therapies with evidence of benefit for a particular symptom for which cannabinoids are being considered should be offered instead of cannabinoids. Some patients may believe that cannabinoids are a treatment for their cancer. Physicians should state that, at present, cannabinoids have an unknown effect on their cancer. The physician of record should discuss the risks of cannabinoids, particularly in patients with a psychiatric history (schizophrenia, bipolar disorder), history of substance use disorder or addiction, cardiac disease, and pregnant women. Cannabinoids do reduce fertility which may imply infertility associated with chemotherapy. A review of medications, including cancer treatment, should be done for possible interactions. Drug-drug interactions

occur predominantly through the CYP2C family of mixed-function oxidases though there is some suggestion that there are interactions at CYP2D6 and CYP3A4. Patients on checkpoint inhibitors or other immunotherapies should discontinue cannabinoids since they prevent checkpoint inhibitor responses and benefits. Cannabis toxicity mimics specific cancer symptoms such that if, for instance, cognitive changes occur or intractable nausea and vomiting emerge, a trial of cannabinoids may be helpful to determine if the symptom is related to cannabinoids.

Conclusion

Cancer pain

We do not recommend the use of cannabinoids for the management of cancer pain outside of a randomized controlled trial (level of evidence: I; grading of evidence: B; category of guideline: recommend).

Given the mixed to largely negative evidence on efficacy based on primary outcomes of randomized trials, the potential of harm, and the availability of other evidence-based therapeutic options with a more favorable benefit-to-risk ratio, we do not recommend the use of cannabinoids in this setting. If considered for use, patients should be carefully monitored, ideally under a clinical trial.

Harms

We recommend against using cannabinoids for any indication in cancer patients undergoing treatment with a checkpoint inhibitor (level of evidence: III; grading of evidence: C; category of guideline: suggestion).

There is retrospective evidence based on two studies of decreased response to checkpoint inhibitors in cannabinoid users with decreased time to tumor progression and decreased overall survival. While this is in limited cancers, the guideline committee recommends against using cannabinoids while further studies investigate this relationship.

We suggest that all patients should be carefully screened and counseled on the potential harms of cannabinoids prior to an initiation where the guidelines support its use (level of evidence: IV; grading of evidence: C; category of guideline: suggestion).

There is limited high-quality data about the short- and long-term harms of cannabinoid use in cancer patients. Evidence from other indications should be considered and discussed, including the risk of drug-drug and drug-disease interactions, cardiovascular risk, neuropsychiatric effects, and hyperemesis. If initiated, the patient should agree to use only the prescribed product to minimize the risk of variable constituents affecting efficacy and potential harms.

We suggest that if cannabinoids have been initiated, all patients should be regularly reviewed for emergent adverse events (level of evidence: IV; grading of evidence: C; category of guideline: suggestion).

Adverse events associated with cannabinoids may mimic other symptoms related to cancer. The committee suggests that physicians should consider the contribution of cannabinoids to new symptoms and the decreased response to cancer treatment associated with the combination of checkpoint inhibitors.

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