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Medical marijuana in the treatment of cancer-associated symptoms

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Abstract

Objective: Previous cancer studies have indicated that medical marijuana addresses a significant unmet need, namely chronic pain treatment and conferring oncology supportive care. However, the clinical research evaluating medical marijuana is preliminary and requires further consideration.

Data Sources: We conducted a PubMed search primarily comprising retrospective and prospective studies, systematic reviews, and randomized clinical trials (RCTs) from approximately 2020–2023. The search included specific terms that incorporated medical marijuana, cancer treatment, cancer-related symptoms, pain management, and side effects.

Data Summary: A total of 40 studies were included in the review, many of which were either of acceptable or good quality. Select investigations indicated that medical marijuana was associated with decreased overall pain levels and improvements in nausea and vomiting. Alternatively, the results from RCTs have found that the benefits from a placebo were equivalent to medical marijuana in both the treatment of cancer-related pain and providing an opioid-sparing effect.

Conclusions: Despite the potential cancer-related benefits derived from medical marijuana, the study design and results for many of the investigations on which the evidence is based, were neither uniform nor conducted via RCTs; hence, the efficacy and appropriateness of medical marijuana in treating cancer-related conditions remain indeterminate.

Keywords

Medical marijuana, emesis, cachexia, cancer pain, supportive care

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Introduction

Marijuana or cannabis is the third most frequently used psychoactive substance worldwide, eclipsed by only alcohol and tobacco.[1] There are reportedly 48 million medical and recreational marijuana users in the United States.[2] In 1996, California became the first state to approve medical marijuana use to treat patients with nausea, weight loss, and pain, and by 2023, 38 states and Washington, D.C., had legalized medical marijuana.[3] While the societal perception of medical marijuana continually improves, there is significant concern about the relevant clinical benefits and corresponding risks for cancer patients who use this therapy.[4]

Abstraction

We conducted an extensive PubMed search primarily comprising retrospective, prospective, systematic review, and randomized clinical trials (RCTs) from approximately 2020–2023, with specific terms that included medical marijuana, cancer treatment, pain management, and side effects. The purpose of this review is to further examine the efficacy and attendant tolerability profile of medical marijuana in the treatment of cancer-associated symptoms.

What is medical marijuana

Medical marijuana is a generic term that incorporates cannabinoids, marijuana, and hemp. Medical marijuana is derived from "Cannabis sativa," "Cannabis indica," and "Cannabis ruderalis." The primary constituent in "Cannabis sativa" is delta-9-tetrahydrocannabinol (THC), which contributes to the manifestation of euphoria and

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relaxation,[5,6] whereas "Cannabis indica" and "Cannabis ruderalis" afford a more tranquil effect.[5–7]

Mechanism of action

The endocannabinoid system comprises cannabinoid CB(1) and CB(2) receptors, which modulate nociceptive information.[8,9] The THC in cannabis binds to the cannabinoid CB(1) and CB(2) receptors, both of which are identified in the central nervous system.[6,10,11] The CB(1) receptors engender a psychoactive, antinociceptive, and anti-hyperalgesic effect, primarily via activation of the inhibitory CB(1) receptors.[12] The CB(2) receptors attenuate pain and inflammation, and are reportedly upregulated in response to chronic pain.[9,13] Cannabidiol (CBD), which originates from the hemp plant and is used medicinally, is non-psychoactive and presumably non-addictive.[10] Moreover, CBD inhibits transient receptor potential vanilloid 1 (TRPV1), which is actuated in response to pernicious stimuli, thereby alleviating pain or discomfort.[13]

Flavonoids also bind to the CB receptors and catalyze the entourage effect, characterized by the synergistic interaction of cannabinoids, terpenes, flavonoids, and other compounds.[14] In particular, terpenes are naturally occurring chemicals identified in both plants and animals that essentially contribute to medical marijuana's distinct aroma. They also possess extensive biologic properties, namely anticancer, anti-microbial, and anti-inflammatory.[15] For example, sesquiterpene, a spicy terpene that interacts with the CB(2) receptors, reportedly confers analgesic, anticarcinogenic, and antiviral effects.[16,17]

The benefits of medical marijuana

Select principal pharmacologic benefits inherent to medical marijuana include spasmolytic, antiemetic, and appetite stimulation.[18,19] Medical marijuana also theoretically engenders antipsychotic benefits and putatively addresses chronic pain and multiple sclerosis symptoms.[6,20–22] Additionally, medical marijuana is reportedly effective at improving several gastrointestinal conditions and symptoms associated with cancer (Table 1 depicts select cancer-related clinical benefits from medical marijuana).

Medical marijuana and cancer-associated pain

Studies have documented that approximately 64% of patients with advanced or metastatic cancer are afflicted with acute or chronic pain,[21,22,26,27] potentially identifying an adjunctive need for medical marijuana. In a prospective analysis, Bar-Lev Schleider et al. recounted that 52.9% of their cancer (e.g. breast, colon, lung) patients initially reported pain levels of 8–10 on a 10-point scale, whereas only 4.6% of patients documented a similar intensity following 6 months of medical marijuana treatment.[28] Johnson et al. evaluated the safety and tolerability of a 1:1 regimen comprising a blend of medical marijuana (THC/CBD) spray versus THC spray alone in 43 breast, prostate, and lung cancer patients.[23] They indicated that THC/CBD was associated with a 24% reduction in pain, although treatment-related side effects (e.g. nausea, vomiting, dizziness, and confusion) were also observed.

In an extensive meta-analysis involving 1459 patients from 20 RCTs that assessed the benefits from cannabis for the treatment of pain, Gedin et al. indicated that in addition to patients deriving significant pain reduction from medical marijuana, they also experienced a clinical benefit from the placebo.[29] Similarly, Hauser et al. in a meta-analysis incorporating 1534 cancer patients from five RCTs, recounted an equivalent (i.e. no additional clinical benefit) outcome from medical marijuana (e.g. oromucosal nabiximols, CBD, or THC alone) in the treatment of moderate and severe pain.[27] Despite the documented pain-reduction benefits from medical marijuana in select investigations, the nonsignificant results from the Cochrane review, meta-analysis, and systematic reviews suggest either an imprecise benefit or potentially the existence of a placebo effect.[23,28,29]

Table 1. Medical marijuana and cancer-associated benefits.

Patient population	Treatment	Benefits	Reference number
breast, lung, and prostate cancer	THC/CBD	Overall pain decreased by 24%	23
Cancer patients of any stage undergoing chemotherapy	CBD with corticosteroids and 5-HT3 antagonists	11% improvement in chemotherapy-induced nausea and vomiting response rates	24
Advanced cancer patients	2.5 mg of THC and 1 mg of CBD	75% of patients demonstrated an improvement in appetite, although the benefit was nonsignificant.	25
Breast, lung, gynecologic, and genitourinary cancer patients	Medical marijuana	Pain and opioid use in patients declined by nearly 45%	26

THC: tetrahydrocannabinol; CBD: cannabidiol.

Nausea and vomiting

Medical marijuana was originally considered a treatment for chemotherapy-induced nausea and vomiting (CINV), based upon the assertion that the therapy effectively inhibited serotonin signaling in the medulla oblongata.[30] Cannabinoid agonists essentially target peripheral CB(1) receptors, thereby decreasing intestinal motility and attenuating emesis.[31,32] Grimison et al. reported an 11% increased response rate for cancer patients undergoing chemotherapy after the inclusion of CBD to traditional anti-emetics (corticosteroids, 5-HT3 antagonists).[24] Currently, the evidence for medical marijuana as an effective anti-emetic is controversial and of low-moderate quality.[33] Moreover, since studies have not exclusively assessed medical marijuana as the primary anti-emetic therapy, the specific impact of medical marijuana as a therapeutic alternative for CINV is inconclusive.[34]

Cancer-associated cachexia

Cachexia is a malignancy-related condition wherein significant skeletal muscle atrophy and fat loss manifest itself, for which dietary counseling and pharmacologic intervention (e.g. progesterone analogs and corticosteroids) may be indicated.[35] In an RCT, Strasser et al. evaluated the impact of a cannabis extract (2.5 mg of THC and 1 mg of CBD vs 2.5 mg THC vs placebo) for advanced cancer patients diagnosed with anorexia-cachexia syndrome.[25] They remarked that the cannabis extract improved the appetite for approximately 75% of patients, although no significant differences were observed among the treatment arms regarding appetite increase and patient quality of life. While there is insufficient evidence to support medical marijuana use as an appetite stimulant or immune system modulator, an ongoing clinical trial (the Cancer Appetite Recovery Study) may further elucidate the potential for medical marijuana as a treatment for cancer patients afflicted with anorexia.[36]

Opioid-sparing benefit

Traditionally, opioids have been indicated for managing cancer-related pain (e.g. chronic and neuropathic), but approximately 15–20% of patients require additional pain relief.[37,38] Therefore, medical marijuana may not only be effective as an adjunctive measure in treating pain, but there is also the potential for an opioid-sparing effect.[26,39]

Sura et al. conducted a retrospective study involving 184 palliative cancer (e.g. breast, lung, gynecologic, and genitourinary) patients to evaluate the characteristics of patients who received medical marijuana via an ambulatory palliative care program.[26] There were 93 (51.5%) patients who underwent at least one dose of medical marijuana, approximately 48% and 45% of whom reported an improvement in pain and a decreased use of opioids, respectively. Conversely, in an RCT, Hardy et al. remarked that CBD oil did not reduce opioid consumption versus placebo for their cancer (e.g. breast, lung, colorectal, hematologic) patients.[40] While medical marijuana is theoretically promising as an opioid-sparing therapy, there is no substantive evidence to warrant the medication's inclusion for cancer-related pain.[41]

Side effects from medical marijuana

Medical marijuana is reasonably well-tolerated in adult and pediatric populations.[42,43] However, vertigo, anxiety, headaches, nausea, and cognitive deficits have reportedly developed following medical marijuana use (Table 2 describes specific side effects associated with medical marijuana), not to mention coughing or bronchitis when the medication is inhaled.[44] In a systematic review and meta-analysis involving more than 2400 patients from 43 RCTs, Avriam and Samuelly-Leichtag documented that 30% of various cancer patients treated with medical marijuana reported at least one side effect (e.g. dizziness, xerostomia, drowsiness) at 6 months, although the symptoms were primarily non-severe.[45] Additionally, the issues of panic attacks, anxiety, psychomotor agitation, and cognitive impairments are potentially a concern with medical marijuana use.[46] Medical marijuana is reportedly safe when clinically supervised, and if indicated, relevant practitioners should be prepared to modulate the starting dose and incorporate titration and/or tapering.

Conclusion

The therapeutic potential of medical marijuana to confer supportive oncology benefits (e.g. improvements in

Table 2. Side effects from medical marijuana.

Patient population	Treatment	Side effects	Reference number
Breast, lung, and prostate cancer	THC/ CBD,[a]	Dizziness, nausea, vomiting, dry mouth, somnolence, and confusion	23
Various cancer patients	Cannabis-based medicine vs placebo	Dizziness, xerostomia, drowsiness	45
Patients with psychiatric and non-psychiatric conditions	Cannabis	Panic attacks, anxiety, psychomotor agitation, and cognitive impairments	46

THC: tetrahydrocannabinol; CBD: cannabidiol.

nausea, vomiting, cachexia, and pain relief) represents a significant unmet need for the nearly two million annual cases of newly-diagnosed cancer.[47] Nonetheless, the primary clinical implications from medical marijuana research studies are indeterminate, especially since many of the studies were not RCTs and included patients who were also using concomitant medications.[20] When considering the increasing number of cancer survivors using medical marijuana, specific cannabis-use guidelines that reflect the manner in which medical marijuana potentially improves cancer patient outcomes, should be developed and instituted.

Author contributions

JM contributed to the conceptualization, supervision, original draft preparation, and final review of the manuscript. MR provided the content analysis, draft preparation, and final manuscript review. RB reviewed the content, participated in draft preparation, and final review of the manuscript. BG provided study supervision, original draft preparation, draft preparation, and final editing of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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