

Pharmacotherapeutic Considerations for Use of Cannabinoids to Relieve Symptoms of Nausea and Vomiting Induced by Chemotherapy

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Abstract

Patients suffering from malignant diseases receive very often highly emetogenic chemotherapy as part of their treatment.

With the aim of assessing the efficacy of cannabinoids in treating chemotherapy-induced nausea and vomiting (CINV), we searched the literature published until April 2020 in Medline/PubMed, Embase, the Cochrane Controlled Trials Register, and in specific web pages. Randomized clinical trials comparing cannabinoids efficacy in managing CINV with that of placebo reported absence of vomiting (3 trials, 168 patients) and absence of nausea and vomiting (3 trials, 288 participants). In comparison with patients receiving other antiemetics, patients receiving cannabinoids reported no nausea (5 trials, 258 participants), no vomiting (4 trials, 209 participants), and absence of both (4 trials, 414 patients). Across all trials, cannabinoids were more effective in relieving the symptoms of nausea and vomiting induced by cytotoxic therapy than placebo was and slightly better than conventional antiemetics. A retrospective review comparing nabilone, dronabinol, delta-9-THC, and delta 8-THC with other antiemetics used to manage CINV in pediatric patients showed that these drugs could also be used as adjuvant antiemetics. Cancer patients on highly emetogenic chemotherapy but with insufficiently effective standard antiemetic therapy can be given cannabis preparations containing similar amounts of tetrahydrocannabinol and cannabidiol, which should be received in strict compliance with the professional guidelines for the treatment of CINV.

Keywords

cannabis, cannabidiol, nausea, tetrahydrocannabinol, vomiting

INTRODUCTION

Patients suffering from malignant diseases are most often treated with highly emetogenic chemotherapy as part of

their treatment. Although cannabinoids have been shown to cause excessive nausea and vomiting, their antiemetic effect in cancer patients experiencing chemotherapy-induced nausea and vomiting is also well-known.

Therapeutic potential of cannabis

In traditional medicine, cannabis preparations have been used for thousands of years in the treatment of various conditions such as chronic pain, spasticity, cancer, seizure disorders, nausea, anorexia, and infectious diseases.¹ As medicinal use of cannabis preparations is widely restricted in many countries for legal and ethical reasons, there is a lack of evidence-based medical information that can corroborate potential benefit of the therapy. Cannabis is used for medical purposes mostly by patients suffering from cancer-related pain. Although medicinal use of cannabis is regarded primarily as use of a symptom-relieving agent in most disorders, cancer patients using the substance tend to perceive it a therapeutic agent capable of curing cancer. The question whether cannabis can be used in the treatment of malignant diseases is rather controversial: there is no published data to show that cannabinoids alone or in combination with conventional therapy can cure any malignant disease in humans. In contrast, there are extremely large numbers of publications that confirm the antitumour effects of cannabis in cell cultures and animal models.²⁻⁵ However, cell cultures and animal models are not sufficient to make rational assumption of therapeutic efficacy of cannabis in humans. There are several positive experiences of the use of cannabinoids in patients with malignant diseases, especially in alleviating the sickness, nausea, and vomiting associated with the use of cytotoxic therapy, pain relief and stimulation of appetite (treatment of cachexia). The benefit of cannabinoid therapy for these indications have been shown in many randomized controlled clinical trials.⁶

A cannabis extract was approved for clinical use for the first time in Germany in 2011 for the treatment of moderate to severe refractory spasticity in multiple sclerosis.⁶ Later, the National Association of Statutory Health Insurance Physicians, and the Drug Commission of the German Medical Association issued the following statement: "The benefit of treatment with cannabinoids for a number of medical indications has been shown in controlled trials in which predominantly standardized and/or synthetic cannabinoid preparations were used. The use of such preparations may therefore be reasonable for patients in whom conventional treatment does not achieve adequate relief of symptoms such as spasticity, pain, nausea, vomiting, or loss of appetite".⁶

Mechanism of action of cannabinoids and the role of endocannabinoid system to relief the symptoms of nausea and vomiting

Cannabinoids possess numerous physiological actions because of binding to cannabinoid receptors in the human body: the CB₁ receptors (predominantly centrally located) and the CB₂ receptors (predominantly with a peripheral position). Both receptors are coupled to G-inhibitory proteins and are linked to signalling cascades in which ade-

nylyl cyclase and cyclic adenosine monophosphate (cAMP) are involved.⁷

The finding that the blockade of one subtype of the serotonin (5-HT) receptor, the 5-HT₃ receptor, may suppress emesis, was a major advance in the control of acute emesis in chemotherapy.⁸ Cannabinoid receptor agonists directly inhibit the function of the peripheral 5-HT₃ receptors.⁹ The first evidence of an interaction between endocannabinoids and 5-HT₃ receptors was detected by the finding that anandamide inhibits 5-HT₃ receptor in rat nodose ganglion cells.¹⁰ But it is also known that 5-HT₃ antagonists are less effective in reducing acute nausea than suppressing acute vomiting. Also, 5-HT₃ antagonists are ineffective in reducing delayed (24 hours later) nausea and vomiting.¹¹⁻¹³

There is plenty of evidence suggesting that the endocannabinoid system can be an effective target in the protection from chemotherapy-induced vomiting, whereas the effect on nausea seems to be limited.¹⁴ It is assumed that the endocannabinoid system inhibits emesis physiologically, by activating the CB₁ and CB₂ receptors localized in the dorsal vagal complex of the brainstem where emetic reflexes are located.¹⁵ After the discovery of CB₁ and CB₂ receptors and the discovery of specific cannabinoid receptor agonists and antagonists, the cannabinoids and the endocannabinoid system are under intensive scientific interest.

Chemotherapy-induced nausea and vomiting (CINV)

Nausea and vomiting (emesis) are important elements in defensive or protective human responses. These responses are sometimes manifested as symptoms of disease, but sometimes there are side effects of various medications, especially chemotherapy used to treat cancer.¹⁶⁻¹⁸ CINV are categorized as acute, delayed, anticipatory, breakthrough or refractory.¹⁹

Many neurotransmitters primarily binding to serotonin, neurokinin-1, and dopamine receptors are involved in this process.^{20,21} The frequency of nausea and vomiting depends primarily on the emetogenic potential of the chemotherapeutic agents that are used.²² Approximately about 45% to 60% of patients with malignant disease experience CINV.²³⁻²⁶ About 70% of patients receiving highly emetogenic chemotherapy are protected from acute emesis by administration of antiemetic therapy. But 30% of patients have symptoms in the delayed phase.²² The primary goal of antiemetic therapy is to prevent CINV²⁷ with appropriate medications.²⁸ There are several antiemetic options for alleviating symptoms of nausea and vomiting and managing CINV: corticosteroids, serotonin receptor antagonists (5-HT₃ antagonists) and neurokinin receptor antagonists (NK₁ antagonists). Also, many alternative medicines such as antihistamines, benzodiazepines, anticonvulsants, and some antagonists of dopamine receptor are used to prevent and manage CINV. Although with newer antiemetics such as ondansetron and aprepitant, vomiting can be well managed, nausea is still not properly controlled.²⁹ The negative side of

medicines that belong to these classes is that they have lower efficacy and are associated with more adverse effects.^{30,31}

The antiemetic effect of cannabinoids in patients with malignant disease treated with highly emetogenic antitumour therapy is well known and proven.³²⁻⁴⁰ The initial incentive for emesis is the release of serotonin (5-HT) from enterochromaffin cells that are distributed across the entire epithelium of the gastrointestinal tract.⁴¹ Observations that the CB₁ agonist WIN 55,212-2 reduced serotonin release evoked by the emetogenic *Staphylococcal enterotoxin*⁴², suggest that inhibiting the serotonin release from enterochromaffin cells might be selectively targeted to reduce emesis triggered by cancer chemotherapeutics.

Cannabinoids achieve their antiemetic effect by acting as agonist predominantly on CB₁ receptors.⁴³ It is important to emphasize that the use of cannabis is not recommended for management of CINV and is not part of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for antiemesis⁴³ because there is not enough medically based evidence and because of legal concerns. And yet, there are many testimonials and positive experiences from the use of cannabis preparations for the treatment of various painful conditions.

Approved cannabis-based medications for CINV

Two medicines: nabilone (Cesamet) and dronabinol (Marinol) are approved for “prevention/treatment of chemotherapy-induced nausea and vomiting” in many countries.

Cesamet (nabilone) is a synthetic cannabinoid for oral administration with therapeutic use as an antiemetic and as an adjunct analgesic for neuropathic pain. It mimics tetrahydrocannabinol (THC). The antiemetic effect of nabilone is caused by interaction with the cannabinoid CB₁ receptor system. It is approved by the FDA for oral administration. It is an analogue of dronabinol, and is available freely in Canada (categorized in level II of controlled substances). Approved indications are: treatment of severe vomiting related to chemotherapy in malignant cases in patients who do not respond adequately to conventional antiemetic therapy (age 18-65 years).⁴⁴ The restriction is required because of the data that disturbing psychotomimetic reactions which are not observed with other antiemetic agents can be expected in a significant number of patients treated with Cesamet (nabilone).

Marinol (dronabinol) is a synthetic THC for oral administration approved also by the FDA. As a prescription medicine, it is approved in the USA, the Netherland and Germany for two indications: treatment of anorexia associated with weight loss in people with acquired immune deficiency syndrome (AIDS) and vomiting caused by chemotherapy in people whose nausea and vomiting have not improved with usual anti-nausea medicines. In the United States, Marinol is considered a non-narcotic drug with a very low risk of physical and mental dependence (categorized as level III of controlled substances).⁴⁵ The mechanism

of action of Marinol is not completely understood. Animal studies with other cannabinoids suggest that Marinol's antiemetic effects may be due to the inhibition of vomiting control mechanism in the medulla oblongata.

Nabilone and dronabinol have shown superiority as dopamine receptor antagonists in the prevention of CINV. There is some evidence that the combination of dopamine antagonist and cannabinoids is particularly effective in preventing nausea.⁴⁶

Nabilone is superior to placebo, domperidone and prochlorperazine but not to metoclopramide or chlorpromazine.⁴⁷ Although dronabinol is approved for the treatment of chemotherapy induced vomiting, some clinical studies show that it can induce emesis.⁴⁸

MATERIALS AND METHODS

For the purpose of this paper, an electronic search was made using Medline/PubMed, Embase, the Cochrane Controlled Trials Register (TRIALS CENTRAL) and a systematic review of randomized clinical trials (RCTs) in order to evaluate the effectiveness and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting in patients with cancer.

A systematic review of RCTs using key words: cannabinoids, nausea, vomiting, CINV, tetrahydrocannabinol and RCTs, conducted till April 2020 screened 198 reports from which only 79 were relevant RCTs, based on title and abstract screening. Seven of them had no relevant information obtained as full-text studies, 28 were in other clinical examinations (pain⁴⁹⁻⁵², HIV/AIDS⁵³, ulcerative colitis^{54,55}, Crohn's disease⁵⁶, epilepsy⁵⁷⁻⁶⁰, multiple sclerosis⁶¹⁻⁶³, autism spectrum disorder⁶⁴, Alzheimer's disease⁶⁵, psychosis⁶⁶⁻⁶⁸), in five emesis was reported, five reports were duplicates (they contained data that had previously been published) (Fig. 1).

We have examined whether there is evidence that cannabinoids has antiemetic effects when given at the same time with emetogenic chemotherapy, how well cannabinoids work for this indication compared to placebo or conventional antiemetics, whether the effect is dose dependent and the profile of adverse effects.

CRITICAL REVIEW

Systematic review of RCTs conducted to August 2000⁶⁹⁻⁷¹

Thirty RCTs that compare efficacy of cannabis preparations (oral nabilone in 16 trials, oral drobaninol in 13 trials and intramuscular levonantradol in one trial) for this indications (nausea and vomiting) to placebo and to other antiemetics (prochlorperazine in 12 trials, metoclopramide in 4 trials, chlorpromazine in 2 trials, thiethylperazine in one

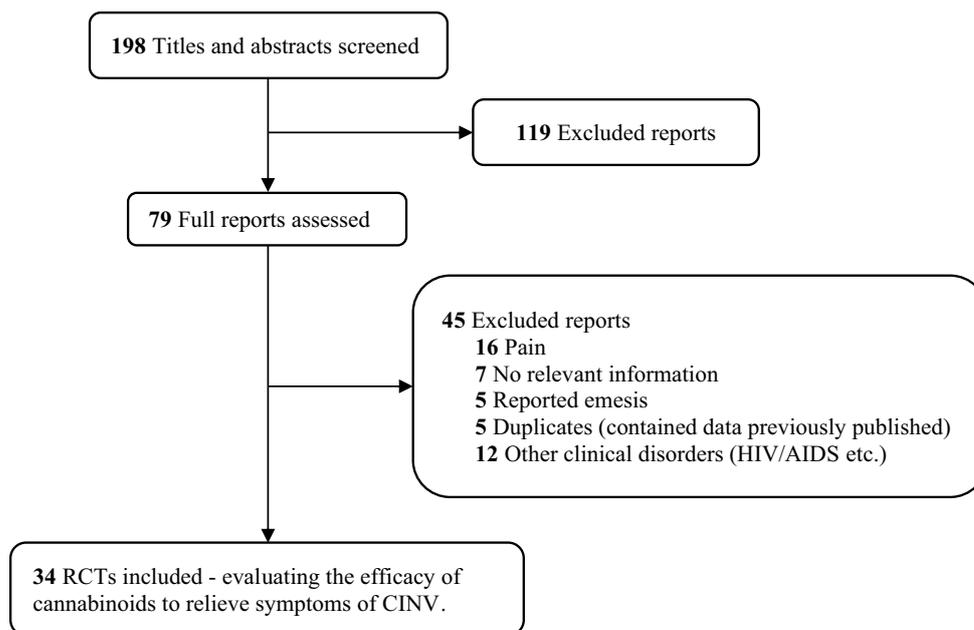


Figure 1. Flowchart of studies through the review process.

trial, haloperidol in one trial, domperidone in 2 trials and alizapride in one trial) which involves 1366 chemotherapy patients analysed. None of these trials compares efficacy of cannabinoids with newer antiemetic drugs such as ondansetron. Nabilone doses ranged from 1 mg per 24 hours (in children) up to 8 mg per 24 hours (in adults). Dronabinol was given according to body surface area in square meters, in doses ranging from 10 mg/m² twice a day to 15 mg/m² six times per day. The observation period was clearly defined as 24 hours (acute antiemetic efficacy).

In comparison with placebo, people report complete absence of vomiting (3 trials, 168 patients) and complete absence of nausea and vomiting (3 trials, 288 participants). The percentage of variability in effect shows low to moderate quality evidence due to heterogeneity. In comparison with other antiemetics, there was no evidence of a difference between cannabinoids and prochlorperazine. Participants report no nausea (5 trials, 258 participants), no vomiting (4 trials, 209 participants) and complete absence of both (4 trials, 414 patients). The quality of evidence was low to moderate.

Side effects in these studies are common for cannabinoids, and although some may be potentially beneficial (euphoria, high sedation) which were reported as a preference for cannabinoids compared with prochlorperazine (7 trials, 695 participants), others were potentially serious (dysphoria, depression, hallucinations, confusion headaches, vision problems, dizziness, abdominal pain, dizziness, nausea, paranoid reaction) and are likely to limit their widespread use. There was weaker evidence for efficacy of cannabinoids in comparison with other antiemetics (metoclopramide, domperidone and chlorpromazine).

Across all trials, cannabinoids were more effective in relieving the symptoms of nausea and vomiting induced by

cytotoxic therapy than placebo was and were slightly better than conventional antiemetics.

The conclusion that can be made from these studies is that cannabinoids tested in these trials indicate that cannabis-based medications may be useful for the treatment of nausea and vomiting caused by refractory chemotherapy as adjuvants for improving chemotherapy-related nausea and vomiting. Potential serious adverse effects, even when taken short-term orally or intramuscularly, are likely to limit their wide use. This was also later confirmed by a meta-analysis done in 2008 which covers the systematic review of the publications up to July 2005 in which nabilone or dronabinol was evaluated with smoking marijuana.⁷³

Meta-analysis performed through Medline and PubMed up to July 2005 in which nabilone or dronabinol was evaluated with "smoking marijuana"

Two systematic reviews of literature^{3,72} identified only two small RCTs in the late 1970s and early 1980s in which nabilone or dronabinol was evaluated with "smoking marijuana". The results of these two studies are contradictory. In one, smoking marijuana was worse than nabilone and not better than placebo, but in the second, smoking marijuana, as a substitute for dronabinol if the patients did not tolerate it (4×1 cigarettes per day, about 17.4 mg THC per cigarette and approximately 70 mg THC/day), showed an antiemetic effect (20 patients with osteosarcoma on a high dose of methotrexate).^{3,72}

In another study, the antiemetic effect of smoked marijuana cigarettes (8.4 mg and 16.9 mg THC per cigarette) was compared to a highly potent antiemetic drug (ondansetron 8 mg). In this study 13 healthy volunteers were included,

and nausea and vomiting were induced by receiving syrup of ipecachuana. This study found that smoking marijuana significantly reduces nausea and slightly reduces vomiting compared to placebo.⁷³

A pilot, randomized, double blind, placebo-controlled phase II clinical trial

Subsequently, a small RCT in 2010, with only 16 patients, indicated that similar effects to relieve symptoms of nausea and vomiting could be expected from nabiximols (Sativex), but Sativex was never further developed and explored in that indication.³⁷ In this placebo controlled (RCT) study, for nabiximols for these indications. Sixteen patients with tumours, receiving highly emetogenic chemotherapy were included, of whom seven were on nabiximols and nine on placebo. At the same time, they were also receiving a standard antiemetic therapy (5-HT₃ antagonists). Nabiximols in this study was titrated as an add-on therapy to standard therapy in a total dose of 8.1 mg THC/7.5 mg cannabidiol (CBD), in three equal actions: 2.7 mg THC and 2.5 mg CBD two hours before chemotherapy, the second dose was given 30 minutes after the first dose (if the patient tolerated well the first dose) and the third dose 120 minutes after the first dose (if the patient tolerated well the second dose). All seven patients received all three doses. Symptoms of nausea and vomiting disappeared after three hours. Side effects of the therapy were reported only in one patient who became anxious, somnolent and confused with visible hallucinations. That patient was excluded from the trial and did not continue to use nabiximol during 4 post-chemotherapy days. The THC doses in this RCT were actually very similar to the recommended doses of dronabinol [6.2 mg THC and 15 mg CBD per day (6 actuations every 4 hours) with the possibility of increasing a single dose up to maximum 130 mg THC and 120 mg CBD per day (8 actuations every 4 hours)]. In total, patients were using nabiximols approximately 3 days (from 1 to 5 days), and the highest average (per day) number of daily actuations was 5 (13.5 mg THC and 12.5 mg CBD). The results were: 5 out of 7 patients did not have delayed vomiting (vs. 2/9 on placebo), 4 out of 7 patients did not have delayed nausea (vs. 2/9 on placebo), and 5 out of 7 patients had no more pronounced nausea (vs. 4/9 at the placebo).³⁷

Dronabinol versus ondansetron in preventing delayed CINV

A completed, still not published, double blind, randomized, placebo controlled, parallel group efficacy study of oral dronabinol alone and in combination with ondansetron versus ondansetron alone has investigated the use of dronabinol versus ondansetron as standard antiemetic therapy in the prevention of delayed CINV.⁷⁴ Patients were randomized into four groups. Group 1 received dronabinol (10 to 20 mg per dose), group 2 received ondansetron (8 to 16 mg per dose), group 3 received combination therapy (10 to 20

mg dronabinol + 8 to 16 mg ondansetron per dose), and group 4 received placebo. The primary response of nausea and vomiting was measured. Total response of nausea and vomiting/retching was defined as no vomiting and/or retching, an intensity of nausea of < 5 mm on the visual analog scale (VAS) and no use of rescue medication. Secondary Outcome Measures in time frame of 5 days were complete responder rate (no vomiting/retching, intensity of nausea of ≤ 30 mm on VAS, and no use of rescue medication), presence or absence of nausea, episodes of vomiting and/or retching and duration of nausea and vomiting and/or retching. Data do support the beneficial effects of dronabinol in managing the symptoms of delayed CINV.

A small 5-day double blind, placebo controlled RCT (a total of 61 patients randomized into three groups) indicates a similar effect of dronabinol compared to ondansetron and the lack of additive effects.⁷⁵ Patients on highly emetogenic chemotherapy, pre-chemotherapy received orally dexamethasone (20 mg), intravenous ondansetron (16 mg) and placebo or dronabinol (2.5 mg). After chemotherapy, the patients randomized to active treatment (dronabinol and/or ondansetron) received dronabinol (2.5 mg) again. At day 2, standard doses of dronabinol (10 mg), ondansetron (16 mg), combination therapy of both or placebo, were administered. From day 3 to day 5 after chemotherapy, the patients were on flexible doses of dronabinol (10-20 mg), ondansetron (8-16 mg), combination of both (10-20 mg dronabinol, 8-16 mg ondansetron) or placebo. The researchers concluded that dronabinol was as effective as ondansetron for the treatment of CINV and the combined therapy with both drugs was not more effective than the therapy with either medicine alone.

Amelioration of CINV by nabilone, dronabinol, delta-9-THC, and delta-8-THC in children

CINV remains an important side effect associated with administration of chemotherapy in pediatrics, too.

In one prospective randomised double blind crossover trial nabilone was compared with oral domperidone for CINV in children. Twenty-three children (aged 10 months to 17 years) with a variety of malignant diseases receiving repeated identical courses of emetogenic chemotherapy were given nabilone therapy. Eighteen out of 23 consecutive eligible children completed the trial. The results showed that nabilone seemed to be superior to domperidone as an effective antiemetic for children on chemotherapy, even for young children. The most common side effects of nabilone were somnolence and dizziness, with one patient having hallucinations.⁷⁶

In another randomized, double-blind, crossover trial, for control of cancer chemotherapy-induced emesis in children, nabilone was compared with prochlorperazine. Thirty children (3.5 to 17.8 years of age) received two consecutive identical chemotherapy cycles. Antiemetics (one cycle with prochlorperazine and another cycle with nabilone)

were given based on body weight and administered 8 to 12 hours before chemotherapy. The total rate of improvement of nausea and vomiting was 70% during the treatment with nabilone and 30% during the treatment with prochlorperazine. Sixty-six percent of children stated that they preferred nabilone, while 17% preferred prochlorperazine. The major side effects (dizziness, drowsiness, and mood swings) were dose related, and occurred when the nabilone dosage was greater than 60 micrograms/kg/d, but individual tolerance to nabilone varied considerably. Lower dosages of nabilone were associated with equivalent efficacy and without major side effects.⁷⁷

From 2000 to 2010 at Riley Hospital for Children at Indiana University Health, the children with malignancy aged 18 or younger receiving highly emetogenic chemotherapy were given at least 1 dose of dronabinol for CINV 1 to 3 hours before chemotherapy and lower dose of other antiemetics. Sixty percent of the patients had a defined positive response to dronabinol. The study concluded that dronabinol seemed to be a viable option as an adjuvant antiemetic in pediatric CINV, but a prospective study that uses patients as its own control is necessary to really define the place of dronabinol in therapy.⁷⁸

In two double blind studies, the anti-nausea and anti-vomiting effects of delta-9-tetrahydrocannabinol in children with cancer on chemotherapy were compared with the effects of metoclopramide syrup and prochlorperazine tablets. THC was found to be significantly better antiemetic agent, but not all patients obtained relief of nausea and vomiting with THC. In some patients, THC increased appetite during chemotherapy.⁷⁹

Delta-8-tetrahydrocannabinol (delta-8-THC) is a cannabinoid with lower psychotropic potency than delta-9-tetrahydrocannabinol. In a clinical trial, delta-8-THC was given to 8 children aged 3-13 years (18 mg/m^2) with various hematologic cancers, treated with different antineoplastic drugs for up to 8 months (the total number of treatments with delta-8-THC was 480). The study showed that vomiting was completely prevented if treatment began two hours before each chemotherapy cycle and continued every 6 hours for 24 hours.⁸⁰

Additionally, adverse events associated with nabilone in a multicenter, retrospective review of pediatric patients ($n=110$) who received nabilone plus a 5-HT₃ antagonist for acute CINV prophylaxis were common but of minor clinical significance [sedation (20.0%), dizziness (10.0%), and euphoria (3.6%)]. However, acute CINV control in children receiving nabilone as a part of their antiemetic regimen was poor in about 50% of patients who experienced complete acute CINV control.⁸¹

DISCUSSIONS

Changes in the laws of many countries to allow legalisation and use of cannabis for medicinal purposes are a signal that cannabis is increasingly recognizable globally and accepted

as something that can really help them to manage a variety of medical conditions. Thus, it is especially important for people to be informed about the possible therapeutic benefits, dosing and adverse effects associated with the use of cannabis.

Thirteen countries of the European Union have already legalized the use of cannabis for medicinal purposes: the Czech Republic, Finland, Romania, Italy, Spain, the Netherlands, France, Austria, Portugal, Germany, Great Britain, Slovenia, and Croatia. Recently, the former Yugoslav Republic of Macedonia also allowed the use of cannabis for medicinal purposes only for four indications: treatment of epilepsy, treatment of spasticity in patient suffering from multiple sclerosis, treatment of anorexia associated with weight loss in people with acquired immune deficiency syndrome (AIDS), and as analgesic for relieve of pain in patient with cancer. For this purpose, 4 different pharmaceutical dosage forms with different ratios of THC and CBD are available as prescription medicines.

But is there any justification for the use of cannabis? Are cannabinoids effective in relieving symptoms of nausea and vomiting induced by cytotoxic therapy? What is the recommended dose and how to titrate it? These are still open questions.

A systematic review of the literature published until April 2020 about the effectiveness and tolerability of cannabis-based medications for CINV in patients with cancer shows that cannabinoids have antiemetic effects when administered concomitantly with emetogenic chemotherapy.

A retrospective review of nabilone, dronabinole, delta-9-THC, and delta 8-THC in comparison with other antiemetics (domperidone, prochlorperazine and metoclopramide) used in pediatric patients shows that these medicines can be used as adjuvant antiemetics.^{60,77,78,80}

But the entrance of new drugs in this indication, especially the newer generations of the 5-HT₃ receptor antagonists and the neurokinin (NK₁) receptor antagonists (aprepitant), redefined the place and importance of cannabinoids - due to the relatively high incidence of significant psychotropic effects and the need for careful dose titration. A meta-analysis including nearly 9000 patients receiving moderately and highly emetogenic chemotherapy showed that they experienced a significant improvement in CINV in the acute, delayed, and overall phases ($p<0.001$) when NK₁ were added to 5-HT₃ antagonists and corticosteroids.⁷⁶ Currently, cannabinoids (nabilone, dronabinol) are considered as third or fourth line of choice, or as the last option in patients in which previous standard treatments do not achieve the desired effect.^{31,37,43,47,82-85}

Unfortunately, a ratio of the effectiveness of cannabinoid compared to the effectiveness of conventional therapy is still unknown. Chronic use of cannabinoids can cause an excessive hyperemesis syndrome characterized by cyclic vomiting without any other recognizable reasons.⁸⁶

In regulatory approved clinical studies, dronabinol is only tested alone and compared with placebo and/or the most common phenothiazines. Only in one or two smaller studies was dronabinol combined with ondansetron. So, in

cases of failure of the standard therapy for management of nausea and vomiting in cancer patients on chemotherapy, dronabinol would be the third or fourth line of therapy, exclusively as monotherapy, because the possibility of add-on therapy is not particularly tested.⁷⁴

However, it is important to emphasize that many patients have a strong preference for cannabinoids. In some cases cannabinoids might be less potent than other available antiemetics, but for some patients they are the only agents that work, and they are the only antiemetics that also increase appetite.⁸⁷

For cancer patients on highly emetogenic chemotherapy for whom the standard anti-CINV therapy (1 or more 5-HT₃ antagonists, corticosteroids) is not sufficient, cannabis preparations containing similar amounts of THC and CBD can be proposed, but they must be taken in accordance with the applicable professional guidelines for the treatment of CINV. Based on the recommendations for the use of dronabinol and nabilone and the described RCT with nabiximols, the initial, pre-therapeutic dose should be fixed (7.5 mg THC and 6 mg CBD divided into 3 equal doses within 60 minutes pre-chemotherapy). The dosage during post-chemotherapy days (up to 4 days after chemotherapy) requires titration of the dose (if necessary) and depends on tolerability. After initial, pre-therapeutic dose, the recommended daily dose can be increased from 16.2 mg of THC and 15 mg of CBD to maximum 45 mg of THC/36 mg CBD (depending on the need and tolerability).

The present review focuses on the findings and quality of systematic reviews of cannabinoids for CINV; it shows that there is no high-quality evidence to recommend when using cannabinoids for the management of CINV.⁸⁶

CONCLUSION

The potential beneficial use of cannabinoids to relieve symptoms of CINV is discussed in this review. In addition, the role of the endocannabinoid system and its significant potential to manage CINV is explained. Keeping in mind the current guidelines for CINV as well as the FDA-approved dronabinol and nabilone in managing CINV and the available data from systematic reviews of RCTs, it can be concluded that there is justification for use of cannabinoids to relieve symptoms of nausea and vomiting induced by cytotoxic therapy. Studies of nabilone, dronabinole, delta-9-THC, and delta 8-THC in comparison with other antiemetics used in pediatric patients show that these medicines can be used as adjuvant antiemetics allowing the reduction of the dose of other antiemetics, and hence the occurrence of adverse effects. Based on the recommendations for the use of dronabinol and the described RCT with nabiximols for the treatment of multiple sclerosis (MS) we should assume that a preparation containing similar amounts of THC and CBD (for example 2.5/2.0 mg per dose), compared to the preparation recommended for patients with MS (2.5/1.25 mg per dose) could be an add-on therapy to

the standard antiemetic therapy (5-HT₃ antagonists, dexamethasone), although an add-on therapy is not particularly tested (two completed, still unpublished studies evaluated dronabinol in combination with a 5-HT₃).

We must also emphasize the fact that there is still no sufficient data to support the routine use of cannabinoids as an antiemetic in all chemotherapeutic modes. Adverse effect profile of cannabinoid also must be seriously considered bearing in mind the increased incidence of adverse effects from cannabinoids compared with conventional antiemetic therapy, especially the psychotropic effects. However, with safe and effective available antiemetics (5HT₃ and NK₁ antagonists), oral synthetic cannabinoids (e.g. nabilone, dronabinol) can be recommended as an adjuvant therapy to relieve symptoms of nausea and vomiting induced by cytotoxic therapy. In cases of failure of the standard therapy for the treatment of nausea and vomiting in cancer patients on chemotherapy, these medicines can be considered as alternative options. Due to the lack of data for efficacy and safety, herbal cannabis (smoking marijuana) cannot be recommended for CINV.

Further research and testing regarding the potential antiemetic effects of cannabinoids for relief of symptoms CINV is needed. A prospective trial using patients as their own controls is necessary to truly define efficacy of cannabinoids for the treatment of acute and delayed nausea and vomiting. Clinical trials in which effects of cannabinoid will be compared with newer antiemetics such as ondansetron is also very important and necessary.

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Фармакотерапевтические рекомендации по использованию каннабиноидов для облегчения симптомов тошноты и рвоты, вызванных химиотерапией

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Резюме

Пациентам, страдающим злокачественными заболеваниями, часто в рамках лечения проводят эметогенную химиотерапию.

Чтобы оценить эффективность каннабиноидов в лечении тошноты и рвоты, вызванной химиотерапией (ТРВХ), мы изучили литературу, опубликованную до апреля 2020 года в данных Medline / PubMed, Embase, Кокрановского реестра контролируемых испытаний и некоторых веб-сайтов. Рандомизированные клинические испытания, сравнивающие эффективность каннабиноидов в контроле ТРВХ с эффективностью плацебо, показали отсутствие рвоты (3 испытания, 168 пациентов) и отсутствие тошноты и рвоты (3 испытания, 288 участников). По сравнению с пациентами, принимающими другие противорвотные средства, пациенты, принимавшие каннабиноиды, сообщали об отсутствии тошноты (5 испытаний, 258 участников), об отсутствии рвоты (4 испытания, 209 участников) и об отсутствии тошноты и рвоты (4 испытания, 414 пациентов). При всех экспериментах каннабиноиды были более эффективны в облегчении симптомов тошноты и рвоты, вызванных цитотоксической химиотерапией, чем плацебо, и были немного лучше, чем обычные противорвотные средства. Ретроспективный обзор, сравнивающий набилон, дронабинол, дельта-9-ТГК и дельта-8-ТГК с другими противорвотными средствами, используемыми при лечении ТРВХ у педиатрических пациентов, показал, что эти препараты также могут использоваться в качестве адъювантных противорвотных средств. Больные раком, получающие высокоэметогенную химиотерапию, но с недостаточно эффективной стандартной противорвотной терапией, могут принимать препараты каннабиса, содержащие аналогичные количества тетрагидроканнабинола и каннабидиола, которые следует принимать в строгом соответствии с инструкциями профессионала по лечению ТРВХ.

Ключевые слова

каннабис, каннабидиол, тошнота, тетрагидроканнабинол, рвота
