



# A critical narrative review of medical cannabis in pediatrics beyond epilepsy, part III: chemotherapy-induced nausea and vomiting and inflammatory bowel disease

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**Abstract:** Cannabis may play a role in alleviating chemotherapy-induced nausea and vomiting (CINV) and improving symptoms of inflammatory bowel disease (IBD). With the surge of interest and legalization of cannabis, its medical use in children for these indications was evaluated. In this third section of a three-part comprehensive review, PubMed, Embase and Clinicaltrials.gov (1966 to May 2020) searches were conducted using the key search terms pertinent to cannabis, CINV and IBD. Only articles pertaining to cannabis and these disease states were extracted and critically evaluated. The high emetogenicity of certain chemotherapies prompts the need for an additional antiemetic therapy. Currently, nabilone and dronabinol are approved for adults with refractory CINV, and refractory CINV or AIDS-associated anorexia, respectively. As such, data support the beneficial effects of these synthetic delta-9-tetrahydrocannabinol (THC) medications as adjunctive therapy to partially or completely control CINV. The adverse effects of THC-based products consisted of drowsiness, dizziness, and mood changes. Data for use in IBD remains limited. For symptomatic control of IBD, survey-based studies have demonstrated that various cannabis products improved appetite, abdominal pain, and nausea, but might be accompanied by increased craving, tolerance, lightheadedness, and drowsiness. Further clinical investigations on its safety and efficacy for CINV (especially for prolonged use and as monotherapy) and IBD are necessary to elucidate the best approach to medically use cannabis in children. Improving healthcare provider knowledge is also important, especially for CINV, to optimize its use.

**Keywords:** Cannabis; medical marijuana; cannabinoids; pediatrics; inflammatory bowel disease (IBD); nausea; vomiting

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## Chemotherapy-induced nausea and vomiting (CINV)

The cannabis plant has been used by many different civilizations for a variety of medical conditions; despite this,

limited clinical research has been performed, partially due to societal barriers and the classification of marijuana as a Schedule I substance. Several factors, including the recent approval of cannabidiol (CBD) by the United States Food

and Drug Administration (FDA) for refractory epilepsy, and the rapid rise of cannabis legalization throughout the United States, have led to a renewed surge of interest in the medical benefits of cannabinoids for many different clinical indications.

As an important component of cancer management, cannabis has been shown to play a role in alleviating side effects of chemotherapy and enhancing palliative care in adults (1). Although there are limited data published on cannabis use in pediatric oncology, a few studies have examined its use for symptomatic management of nausea and vomiting associated with chemotherapy in children, which affects 70% of pediatric patients with cancer (2-5).

Emesis is most commonly caused by a disturbance in the gastrointestinal tract in response to consuming what the body considers a toxin such as bacteria, food, or medications like chemotherapy. In the epithelium of the gastrointestinal tract, the primary trigger of this pathway is the release of serotonin from the enterochromaffin cells, activating 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors in the vagal afferent nerves. When stimulated, this initiates a series of biochemical processes impacting the motor responses and activating the respiratory, gastric, salivary, esophageal, and laryngeal centers in the dorsal vagal complex of the brain (6). The primary neurotransmitters responsible for eliciting emesis behaviors are serotonin, dopamine, and substance P; hence conventional pharmacologic therapy for CINV was developed to target the activity of these neurotransmitters and includes medications that are antagonists of the serotonin, dopamine 2 (D<sub>2</sub>), and substance P/neurokinin-1 receptors (7).

According to the *Children's Oncology Group Supportive Care Endorsed Guidelines*, each stage of increased emetogenicity (low, moderate, high) of chemotherapeutic regimens prompts the need for an additional antiemetic agent. Children receiving moderately emetogenic chemotherapy (MEC) should be treated with a 5-HT<sub>3</sub> receptor antagonist (e.g., granisetron, ondansetron, or palonosetron) and a corticosteroid (e.g., dexamethasone). For highly-emetogenic chemotherapy (HEC), the recommended treatment consists of a 5-HT<sub>3</sub> antagonist, dexamethasone, and a neurokinin-1 receptor antagonist (e.g., aprepitant). If the patient has a known or suspected hypersensitivity to any of these medications, an alternative agent is suggested (8). D<sub>2</sub> antagonists, such as the phenothiazines, have not been considered first line therapy since the introduction of the newer agents as mentioned.

We present the following article in accordance with the

Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/pm-20-70>).

### *Mechanistic pathway*

The recent discovery of the endocannabinoid system (ECS) has elucidated new ways to regulate the spectrum of anticipatory, acute, delayed, breakthrough, and refractory nausea and vomiting (9). The ECS, comprising the cannabinoid receptors 1 and 2 (CB<sub>1</sub> and CB<sub>2</sub>), the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and the enzymes responsible for synthesis and catabolism of AEA and 2-AG, is thought to be involved in the regulation of nausea and vomiting. CB<sub>1</sub> is widely distributed in the brain and periphery, including neurons in the brain regions involved in the control of nausea and vomiting, and is thought to also be expressed on enterochromaffin cells in the gut and afferent vagal neurons (6,9). The proximal location of CB<sub>1</sub> and 5-HT<sub>3</sub> receptors in enterochromaffin cells, vagal afferent nerves, and various regions of the brain suggests that CB<sub>1</sub> receptor agonists may be involved with the regulation of emesis. It is postulated that agonists of CB<sub>1</sub> receptors in the gastrointestinal epithelium may inhibit the release of serotonin (10), and CB<sub>1</sub> expression in the dorsal vagal complex may contribute to mediation of emesis (11). As such, the relationship between the 5-HT<sub>3</sub> receptor systems and the CB<sub>1</sub> agonists, AEA and THC, suggests that the ECS has the potential to be manipulated for emesis management using exogenous cannabinoids (6).

### *Clinical studies of synthetic delta-9-tetrahydrocannabinol (THC)*

As potential antiemetic agents, THC and THC analogues have been the most investigated of the cannabinoids. Many of the earlier published studies investigated nabilone (Cesamet<sup>TM</sup> Valeant, Costa Mesa, CA), an oral synthetic cannabinoid analogue of THC, with a molecular structure slightly different from that of THC. Nabilone has demonstrated fewer episodes of nausea and vomiting in adults receiving MEC (6), shown to be comparably effective for HEC (12) when compared to D<sub>2</sub> receptor antagonists, and was approved by the FDA in 1985 for adults with CINV refractory to conventional antiemetic therapy (13).

Ekert *et al.* investigated the use of oral THC 10- to 15-mg/m<sup>2</sup> versus metoclopramide or prochlorperazine 5- to 10-mg for the relief of CINV in children in two double-blind randomized controlled trials. Both trials demonstrated

reduced nausea and vomiting in the participants receiving THC (14) (*Table 1*). Chan *et al.* conducted a double-blind, randomized, crossover study of 30 children receiving two courses of identical chemotherapy, measuring the rate of reduction of retching and vomiting, and the overall rate of improvement of retching and vomiting as subjectively characterized by the subject and their parents. Results showed that subjects experienced a 70% overall rate of improvement of vomiting with nabilone 0.5- to 2-mg twice daily, in contrast to 30% with 2.5- to 10-mg twice daily prochlorperazine ( $P=0.003$ ). Interestingly, 66% of participants demonstrated a preference for nabilone, while 17% preferred prochlorperazine ( $P=0.015$ ). The most common side effects reported were dizziness and drowsiness (15) (*Table 1*). A similarly designed study evaluated the efficacy of oral nabilone 0.5-mg twice daily compared to oral domperidone 1-mg three times daily in 18 children receiving chemotherapy. On a scale of 0–3 (with 3 being the worst), patients reported a statistically significant reduction in nausea with nabilone compared to domperidone ( $P=0.01$ ) as well as a reduction in mean number of vomiting episodes ( $P<0.01$ ). As in the Chan trial, study participants demonstrated a preference for nabilone over domperidone. Drowsiness was the most common adverse effect (16) (*Table 1*).

A 5-year, multicenter, retrospective review described the safety and efficacy of nabilone as adjuvant treatment for CINV prophylaxis in children receiving >1 dose of chemotherapy. Most of the participants (109/110) who received MEC or HEC were treated with a combination of nabilone and 5-HT<sub>3</sub> antagonists, and 58% of those were also given an additional antiemetic. Results demonstrated that over 50% of all patients experienced complete chemotherapy-induced vomiting control while 31.8% had partial control. Adverse effects were experienced by 37 (34%) patients who reported sedation and dizziness as the most common effects (17) (*Table 1*). The contribution of the therapeutic effect of nabilone was difficult to determine, since all patients were treated with multiple antiemetics.

Dronabinol (Marinol® Solvay Pharmaceuticals, Marietta GA) was the second synthetic THC medication approved by the FDA for adults with CINV, differing from nabilone in that its structure is identical to THC (18). Similar to nabilone, dronabinol has demonstrated fewer episodes and shorter durations of nausea and vomiting when compared with D<sub>2</sub> receptor antagonists as monotherapy and in combination for MEC. In a 10-year retrospective chart review of 55 children receiving MEC or HEC and more than one dose of dronabinol, response to dronabinol was

measured as good, fair, or poor, based on the number of emesis events. A median of 3.5 doses were received per patient per hospital visit (range, 1–129). Regardless of the emetogenic risk of regimen, 60% of patients reported a good response, 13% had a fair response, and 27% were poor responders. Tolerability, indirectly measured by continuation as outpatients, was reported by 62% of patients. Although there were limitations in this review, including the absence of nausea severity rating and lack of control of concomitant antiemetics, this retrospective study demonstrates the potential use of cannabinoid-based therapy in the pediatric CINV population (19) (*Table 1*). It is notable that although the dosing guidelines state 5 mg/m<sup>2</sup>, the most common dose was 2.5 mg/m<sup>2</sup>, suggesting perhaps that future studies could investigate lower doses for efficacious therapy in pediatric CINV (18).

Delta-8-THC is an isomer of delta-9-THC, differing in structure only by the location of a double bond, incurring enhanced chemical stability and reduced intoxicating effects. Although also naturally occurring in the cannabis plant, the quantities of delta-8-THC produced are so limited that the chemical is usually prepared in a laboratory using various techniques (20,21). It has been hypothesized that higher doses of delta-8-THC (18 mg/m<sup>2</sup>) used in children with CINV may optimize therapeutic benefit with minimal side effects associated with the same doses of delta-9-THC (21). One study investigated the use of delta-8-THC in eight pediatric patients with CINV (21) (*Table 1*). Preliminary results indicated that when delta-8-THC was initiated as a pre-medication two hours before chemotherapy and repeated every six hours, prevention of vomiting was observed during 480 cycles. Despite this promising observation, these conjectures need to be further explored in clinical studies to ascertain the benefits of delta-8-THC over delta-9-THC.

The primary nabilone and dronabinol studies described above were conducted over 30 years ago, prior to the advent of more current antiemetics. To date, there are no pediatric studies comparing the efficacy of synthetic THC against either 5-HT<sub>3</sub> or neurokinin-1 receptor antagonists, nor is there any evidence for the use of other cannabis products, including plant-derived cannabis and CBD, for CINV management in children.

### Summary statement

The high emetogenicity of chemotherapy, severely affecting pediatric oncology patients, has led to research efforts to

Table 1 Studies of cannabis for CINV in pediatrics

Author(s)	N	Population	Mean age (range), years	Study design	Dose <sup>§</sup>	Dosing regimen	Adverse effects <sup>†</sup>	Outcomes
Ekert <i>et al.</i> , 1979	19	PM <sup>†</sup>	11.0 <sup>¶</sup> (5 to 19)	DB RCT, crossover	THC 10 mg/m <sup>2</sup> ; metoclopramide 5 or 10 mg (by BSA)	-2, 4, 8, 16, 24 hours around CTX; placebo given at +4 hours	None reported	Reduced nausea and vomiting compared to metoclopramide
Ekert <i>et al.</i> , 1979	14	PM <sup>†</sup>	14.0 <sup>¶</sup> (6 to 19)	DB RCT, crossover	THC 10 mg/m <sup>2</sup> ; prochlorperazine 5 or 10 mg (by BSA)	-2, 4, 8, 16, 24 hours around CTX; Placebo given at 4 hours	None reported	Reduced nausea and vomiting compared to prochlorperazine
Chan <i>et al.</i> , 1987	30	PM <sup>†</sup> , history of CINV	11.8 (3.5 to 17.8)	DB RCT, crossover	Nabilone 0.5–1 mg (by weight); prochlorperazine 2.5–5 mg (by weight)	8–12 hours prior to CTX then BID or TID	Drowsiness (67%), dizziness (50%), euphoria, ocular irritation, hypotension	Reduced retching and vomiting (60%), overall improvement of retching and vomiting (21%), patients' drug preference (20%), compared to prochlorperazine
Dalzell <i>et al.</i> , 1986	23	PM <sup>†</sup> , 2 identical cycles scheduled	7.9 (0.8 to 17)	DB RCT, crossover	Nabilone 0.5–2 mg (by weight); domperidone 5–15 mg (by weight)	24 hours prior to CTX then nabilone BID or TID, or domperidone TID	Drowsiness (55%), dizziness (35%), elevated mood, hallucinations (n=1)	Reduced nausea severity and vomiting compared to domperidone
Polito <i>et al.</i> , 2018	110	PM <sup>†</sup>	14.0 (1.1 to 18)	5-year retrospective chart review	Nabilone 0.019/kg initial dose with 5-HT <sub>3</sub> antagonist	Once daily (5%); BID (83%); TID (3%)	Sedation (20%), dizziness, euphoria	Complete control of vomiting in ≥50% of children; 31.8% partial control
Elder and Knoderer, 2015	58	PM <sup>†</sup>	13.9 (6 to 18)	10-year retrospective chart review	Dronabinol ≤2.5 mg/m <sup>2</sup>	Scheduled in 55%; PRN in 45%	None reported	Positive response (0–1 episodes of vomiting) in 60% of children
Abrahamov <i>et al.</i> , 1995	8	PM <sup>†</sup> , hematological	6.6 (3 to 13)	Open-label	Delta-8-THC 18 mg/m <sup>2</sup> , 4 total doses	2 hours prior to CTX then QID	Irritability (n=2), euphoria (n=1)	Complete success preventing nausea and vomiting

<sup>†</sup>, any pediatric malignancy; <sup>‡</sup>, listed in descending order of frequency; percentages only listed if ≥20%; <sup>§</sup>, oral monotherapy unless otherwise indicated; <sup>¶</sup>, median ages reported as mean ages not reported. BID, two times daily; CTX, chemotherapy; PM, pediatric malignancy; PO, by mouth; PRN, as needed; QID, four times daily; TID, three times daily.

evaluate if cannabinoids are effective as agents for the use in CINV. Current clinical studies are limited and the few trials that have been conducted have been restricted to the FDA approved agents, nabilone and dronabinol, with one study evaluating the THC isomer, delta-8-THC. There are no current studies evaluating a plant-derived cannabis product. Albeit their optimal use remains unknown, nabilone and dronabinol have shown promising results in the prevention of CINV, either partially or completely, when used in children as mono- or adjunctive therapy. Importantly, patients often report a subjective preference for the THC product when compared to another antiemetic.

The safety profiles of the THC-based products were consistent among studies, with drowsiness and dizziness reported as the most relevant side effects (14-17,22). However, the lack of studies comparing cannabis to conventional antiemetic regimens, such as newer 5-HT<sub>3</sub> antagonists or aprepitant, and the absence of the evaluation of other cannabis products, including CBD, for emesis control, prompts the need for further investigation, especially integrating larger sample sizes. Specifically, further research is needed to determine the optimal dose, dosage form, drug-drug interactions, and safety of prolonged use of the products in the pediatric population.

The American Academy of Pediatrics opposes pediatric cannabis use in nearly all circumstances; however, they support its use in “children with life-limiting or seriously debilitating conditions”, which may arguably include CINV. The negative impact of CINV on a child’s life should not be underestimated as up to two-thirds of the patients may experience CINV (23). While current studies are inconclusive, the medical use of cannabis in children with CINV is largely based on clinical discretion (5). As such, the healthcare provider-patient relationship as well as the provider’s knowledge of cannabis use in childhood cancer are crucial to prescribe cannabis in specific patients who may most likely benefit. Interestingly, Ananth and colleagues surveyed 634 provider perspectives on medical cannabis in children with cancer, and reported that 33% received inquiries regarding cannabis each month and 92% were willing to consider it as a supportive therapy (24). This underlines the importance and need for practitioners to be educated on the benefits and harm of medical use of cannabis.

### **Inflammatory bowel disease (IBD)**

IBD is an immune-mediated chronic intestinal condition consisting of two primary types: ulcerative colitis (UC)

and Crohn’s disease (CD). The pathogenic hypothesis is a dysregulation of the three major components of gut homeostasis: microbiota, intestinal epithelial cells, and immune cells in the tissues. Primary symptomatology includes diarrhea, rectal bleeding, anemia, abdominal pain, and nausea and vomiting (25). Pediatric practitioners must not only focus on simply treating IBD itself, but also consider pediatric attributes such as growth, proper weight gain, skeletal development and puberty, as 20–25% of patients develop it in childhood or adolescence (26).

Currently, gastroenterologists rely on a stepwise approach using FDA approved medications to treat IBD, following the American Gastroenterological Association (AGA) guidelines characterizing drug therapy depending on the type and severity of disease. These include aminosalicylates (i.e., sulfasalazine, mesalamine), glucocorticoids, thiopurines (i.e., 6-mercaptopurine, azathioprine) and biologics (i.e., TNF- $\alpha$  antagonists, such as infliximab) (27,28). Unfortunately, these regimens are often unsuccessful, prohibitively expensive, and are accompanied by a high risk of adverse events, such as immunosuppression, infection, malignancy, and anaphylaxis.

### *Mechanistic pathway*

Evidence suggests a correlation between ECS tone and IBD pathology. As reviewed extensively by Gyires *et al.* (29), CB<sub>1</sub> receptors have been identified in the colonic epithelium, smooth muscle, and the submucosal myenteric plexus. Similarly, CB<sub>2</sub> receptors have been located in the gut epithelium, subepithelial macrophages, and plasma cells. Expression of both receptors has been shown to be elevated in the inflamed gut. In addition, endocannabinoid expression, particularly anandamide (AEA), is also altered in patients with IBD. It has been shown that AEA levels are increased in colonic samples of UC patients in early disease, and reduced at later time points, suggesting the protective role of AEA in early inflammatory processes, but a deteriorating role in later disease (30). It is likely that AEA levels are reduced in prolonged inflammation due to the decreased expression of the AEA precursor and increased expression of fatty acid amide hydrolase (FAAH), the enzyme required for AEA degradation (31,32). Furthermore, the absence of alterations in the levels of a second endocannabinoid, 2-arachidonoylglycerol, in gut inflammation implies the lack of importance of this endocannabinoid in IBD (30,32). Overall, evidence is suggestive of a role of exogenous cannabinoids in the

manipulation of the ECS for the potential treatment of IBD symptomatology (33). In particular, CBD has been shown to display anti-inflammatory properties in animal models (34). Because CBD is known to have little to no affinity for the CB receptors, it is suggested that its anti-inflammatory effects are due to the disruption of the enzymatic breakdown of AEA by FAAH, leading to elevated AEA levels, resulting in the indirect activation of CB<sub>1</sub> and CB<sub>2</sub> receptors. In addition, CBD reduces neutrophil proliferation and inhibition of proinflammatory cytokine release, such as interleukin-1, interleukin-6, and interferon gamma from microglial cells (34).

### *Clinical studies of various cannabis products*

Although the AGA does not provide guidance on cannabis use, patients frequently supplement their IBD therapy independently with the perception of added medical benefits to control their symptoms (35). Research on the use of cannabis in adults has shown promise for symptom relief; however, clinical trials in the pediatric population are lacking (36,37). Although one small study showed safety, but not efficacy when using low dose CBD for patients aged 20–75 with Crohn's disease (38), there are currently no retrospective or prospective controlled studies for IBD in pediatric patients. Following is a review of three survey and questionnaire studies that evaluated cannabis use in pediatric IBD patients.

Hoffenberg *et al.*, in 2018, conducted a descriptive cross-sectional study of 99 adolescents and young adults with IBD. Patients completed questionnaires that included self-report data on appetite, pain, quality of life, depression, anxiety, and cannabis use. Approximately 32% of subjects reported cannabis use in the past six months and/or ever and were designated as 'ever-users'. Twenty-nine of these 'ever-users' provided responses to the use-pattern questions, with 82% reporting using cannabis daily or weekly. Furthermore, 57% of the 30 'ever-user' patients acknowledged cannabis use for at least one medical condition and reported symptomatic relief for improved appetite (23%), pain (53%), abdominal cramping (37%), and nausea (27%). The most common mode of cannabis consumption was smoking, followed by edibles, dabbing, and vaping. One or more problems were reported by 37% of patients and included craving (20%), tolerance (17%), and using larger amounts for longer than intended (17%) (39).

In a second survey-based study, Hoffenberg *et al.* evaluated a subset of the same group of IBD patients,

comparing those who had used oral or sublingual cannabis oil with those who were cannabis non-users in the prior six months. Cannabis oil was used by 15% of 99 patients who were enrolled. Nine of the 15 subjects who responded to the survey endorsed better sleep, decreased nausea, and increased appetite, while two reported improved mood and decreased anxiety. There was no consistency with concentration ratios of CBD and THC or routes of administration (sublingual, oral pills, tinctures, and beverages) (40).

In a prospective survey conducted in 2017, Phatak *et al.* reported on cannabis use in 53 young adults diagnosed with IBD. Thirty-seven (70%) patients used cannabis either currently or in the past, and of those, 70% did not discuss use with their healthcare provider. The most common method of consumption was smoking, followed by edibles. Twenty-four of 37 (65%) patients indicated a medical condition for use and most reported either moderate or complete symptomatic relief for poor appetite, abdominal pain, nausea, and diarrhea. Adverse effects were reported by seven of 37 (19%) and were identified as fear, paranoia, lightheadedness, laziness, drowsiness, loss of focus, poor diet, lethargy, and addiction (41).

### *Summary statement*

The descriptive studies of cannabis use, based on self-reported questionnaires, were deficient in both objective measures of efficacy that incorporated biomarkers and measures of concomitant prescription IBD therapy. However, these surveys highlight the fact that, regardless of healthcare provider consultation or knowledge, adolescents and young adults are using cannabis for IBD symptom relief and associated use with a perceived improvement in symptoms and quality of life. As such, it is imperative not only to advocate the need for and conduct clinical studies, but to ensure adequate knowledge of healthcare providers in order to provide comprehensive care of patients.

Guidance on cannabis use from professional organizations, such as the AGA, is non-existent. Although the American Academy of Pediatrics opposes cannabis use for all diseases outside of the FDA-approved regulatory process, there are provisions for debilitating conditions in which current therapies are inadequate (42). Despite documentation of the involvement of cannabinoids and the ECS in gut homeostasis and the apparent self-treatment of patients, clinical evidence at this time does not support the recommendation of cannabis products for the treatment of

IBD in the pediatric population. However, care providers are urged to communicate openly with their pediatric patients and their caregivers to determine if cannabis supplementation is being used. Informed providers can then discuss the benefits and risks of use, as well as monitor for side effects and drug interactions. Informed providers can also assist patients in obtaining a reliable product from a reliable source and educate about the benefits of choosing an oral or sublingual product over smoking.

## Conclusions

Current published literature indicates a surge of interest in the use of cannabis for symptomatic management of CINV and IBD. Pharmacological evidence demonstrating the intricate network of endocannabinoids and cannabinoid receptors in areas of the central and peripheral nervous systems involved with CINV, and the gastrointestinal tract suggest the need for further research into cannabis for treatment considerations. Based on the studies reviewed in this paper, it is reasonable to consider cannabis as adjunctive therapy to accompany conventional CINV regimens; however, more research is needed to determine its use as monotherapy. The published literature remains too limited to recommend cannabis-derived products for IBD. The safety profile of cannabis-derived medications has shown to be acceptable, with few reported side effects.

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appropriately investigated and resolved.

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