

Cannabis-Induced Gastrointestinal Tract Symptoms in the Adult Population: A Systematic Review

Helen Senderovich^a Christopher Meaney^b Srishti Vashishtha^c

^aDepartment of Family and Community Medicine, Geriatrics and Palliative Care, Baycrest University of Toronto, Toronto, ON, Canada; ^bDepartment of Family and Community Medicine, University of Toronto, Toronto, ON, Canada; ^cSchool of Medicine, University College Dublin, Dublin, Ireland

Highlights of the Study

- Recreational and/or medicinal cannabinoid use is associated with various adverse effects, prominent amongst which are gastrointestinal.
- Cannabis-induced gastrointestinal side effects include nausea, vomiting, diarrhoea, and adult intussusception.
- Recognition of cannabis-induced gastrointestinal side effects is important for the implementation of evidence-based guidelines for healthcare provider use and for safe prescribing practices.

Keywords

Cannabinoids · Gastrointestinal symptoms · Adult population

Abstract

Objective: Cannabinoid usage is widespread in the self-management of various medical ailments. However, adverse effects have been reported with use, especially pertaining to the gastrointestinal system in adults and aged patients. These range from nausea, vomiting, bloating, or abdominal pain. This systematic review of previously reported cannabis-induced gastrointestinal symptoms in the adult population from the literature provides an analysis of relevant data to enhance knowledge and awareness of this topic. **Methods:** PubMed, Ovid MEDLINE, Cochrane Central,

EMBASE, and Google Scholar databases were searched for relevant studies published from inception to March 2023.

Results: The search yielded 598 results, of which 13 were deemed relevant and underwent further review. These included two systematic reviews, one retrospective cohort study, one retrospective chart review, two cross-sectional studies, one survey, and six case reports. The Cochrane Risk Tool for bias analysis was applied where relevant. The total number of people in the studies selected for analysis was 79, 779. Twelve out of the thirteen included studies reported some type of gastrointestinal tract symptoms experienced in medical and/or recreational cannabis users ranging from nausea, vomiting, diarrhoea, abdominal pain to adult intussusception. **Conclusion:** Potential limitations include small sample sizes, variation in research methodologies, varied studied designs, and limited availability of data on

specific populations such as geriatric users. Further research is warranted to add to current evidence pertaining to this emerging topic of significance, fill the broad knowledge gaps and contribute to evidence-based guidelines for healthcare professionals, ensuring safe prescribing practices and provision of quality care.

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Introduction

According to the 2022 World Drug Report released by the United Nations Office on Drugs and Crime (UNODC), in 2020 an average of 209 million people aged 15–64 were utilising cannabis in some form [1]. Accounting for a significant portion of the global population of adults in terms of use, this makes cannabis the most widely used drug worldwide. Notably, this is a 23% increase from the number of adult cannabis users in 2010 (170 million) [1]. “Cannabis” collectively refers to products derived from the plant genus *Cannabis* [2]. Cannabinoids are the active ingredient, and while over 100 have been identified, tetrahydrocannabinol (THC) and cannabidiol (CBD) are of significance. The effects of cannabis in the human body are mediated by binding of the cannabinoids to the endocannabinoid receptors of which there are two, CB1 and CB2 [3]. CB1 receptors are found in both central and peripheral nervous systems, and CB2 receptors predominate in immune cells [3]. Cannabinoids exert their effects by binding to these receptors producing the “desirable” effects such as blocking the release of pain-inducing neurotransmitters in the central nervous system [4]. The endocannabinoid system is also present in the gastrointestinal tract (GIT). CB1 receptors can be found within the myenteric and submucosal neurons of the GIT, while CB2 receptors are primarily situated on inflammatory and epithelial cells [4]. Within the GIT, two primary endocannabinoids, namely anandamide and 2-arachidonoylglycerol, are present. These endocannabinoids are synthesized as needed and serve as signalling molecules that bind to cannabinoid receptors. Activation of CB1 receptors can result in a decrease in GIT motility, whereas activation of CB2 receptors in immune cells can regulate inflammation within the digestive system [3, 4]. This ligand-receptor interaction is also known to produce detrimental effects, responsible for the unwanted symptoms exhibited in cannabis users.

Harmful and inappropriate patterns of cannabis use have been posited to have increased recently during the COVID-19 pandemic, as well as with legalisation of cannabis in certain areas, leading to altered perceptions of harm [5]. This increase in cannabis utilisation has led to an increase in cannabis-related side effects and associated hospitalizations. Cannabis use can be medical or recreational in nature. Medical use includes but is not limited to, chemotherapy associated nausea and vomiting, neuropathic pain, multiple sclerosis, and appetite stimulation [2]. While cannabis has shown promise in managing certain medical conditions, it is not without the possibility of adverse effects. Acute and chronic cannabis use is associated with a variety of side effects across cardiovascular, respiratory, immune, and neurological systems [6].

Recently, research has slowly begun to highlight the GIT adverse effects of cannabis use [7]. Some studies define GIT illness as experiencing GIT symptoms associated with vomiting or diarrhoea that start in the 30 days prior to being surveyed [8]. GIT adverse effects range in severity and include symptoms such as dry mouth, mouth ulceration, nausea, vomiting, constipation, and diarrhoea. A more severe adverse effect includes cannabis hyperemesis syndrome (CHS), a condition that leads to repeated and severe vomiting episodes, first reported by Allen and colleagues in 2004 [9, 10]. The presentation of CHS includes chronic nausea, vomiting, and abdominal pain originating in the epigastrium and radiating outwards [11]. The clinical course has three phases: prodrome, hyperemesis, and recovery. Reported incidents of CHS mostly include males who engaged in cannabis use daily in their teenage years and developed symptoms after this chronic and heavy use [12]. As cannabis is marketed as a medicinal product for various uses in many countries, there is data available regarding adverse effects. One example is SATIVEX[®], a buccal spray indicated for symptomatic relief of spasticity in patients with MS. Treatment emergent GIT adverse events for SATIVEX[®] in placebo-controlled studies in patients with MS occurring at 1% or above more frequently than in placebo included nausea (9.6%), dry mouth (6.1%), diarrhoea (5.5%), vomiting [3, 5], and constipation (2.4%) to name a few [13]. Similarly, EPIDIOLEX[®], an oral CBD solution indicated for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older, presents with GIT side effects of decreased appetite (22%), diarrhoea (20%), weight loss (5%), gastroenteritis (4%), and abdominal pain (3%) when compared to placebo [14].

With increased use of cannabis in the adult population, a lack of research and knowledge pertaining to cannabis-induced GIT symptoms, and an increased number of patients experiencing them, this is a topic of importance to researchers, physicians, and patients alike. Awareness of this issue will assist in ensuring there are appropriate prevention and management strategies in place when encountered.

Objective

The aim of this systematic review was to identify and synthesise relevant information regarding adverse GIT symptoms of cannabis utilisation in the adult population. We hoped to contribute to our understanding and practical skills by consolidating documented instances of gastrointestinal side effects (beyond just nausea and vomiting) linked to cannabis use. As a result, it will equip healthcare professionals with current data that is vital for enhancing patient care. This is the only study to date that has synthesized, summarized, and isolated cannabis-induced GIT symptoms. Additionally, this review underscores the limited availability of data in vulnerable populations, particularly the geriatric population. It emphasises the need for more research because the use of cannabis and its potential adverse effects among the elderly are most likely not fully reported or understood.

Methods

A systematic review was conducted utilising PubMed, Cochrane Central, Ovid MEDLINE, EMBASE, and Google Scholar. The keywords included in the search were limited to “cannabinoid,” “THC,” “CBD,” “gastrointestinal tract symptoms,” “nausea,” “vomiting,” “abdominal pain,” and “adult.” The literature search and review process was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [15]. A data extraction form was created using Microsoft Excel to compile and summarise relevant studies. Eligibility assessment using inclusion and exclusion criteria was performed by two independent reviewers and included assessments were assessed by both reviewers. Duplicates were removed using EndNote X9 before applying the inclusion and exclusion criteria. Inclusion criteria were established in line with the study objective, and relevant studies underwent data extraction and analysis. The Cochrane Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I) was used to assess the risk of bias in non-randomized studies [16]. A table was created to visually display results of individual studies and syntheses (Table 1).

Inclusion Criteria

Studies written in the English language from June 2008 up to March 2023 focussing on both male and female adults 18 years of age and older and detailing recreational or medical cannabinoid use and its related GIT symptoms were included in this review. Both peer-reviewed and non-peer reviewed studies were evaluated and all study designs were included in the evaluation. The PICO tool was used to inform and guide the keywords used in the search.

Exclusion Criteria

Non-English language studies and studies conducted on non-human populations were not evaluated. Studies not describing GIT symptoms associated with cannabis use, or studies focussing on populations under the age of 18 were not evaluated.

Results

Search Results

Relevant studies underwent data extraction and analysis. An initial search yielded 598 references (33 from PubMed, 19 from Cochrane Central, 144 from EMBASE, 122 from Ovid MEDLINE, and 280 from Google Scholar) that matched predefined search parameters. Of these, 316 duplicates were removed using the EndNote deduplication feature. The remaining 282 studies were screened further for relevance, of which 269 studies were excluded as a GIT symptom was not described in association with cannabis use. The remaining full-text 13 studies were reviewed, and two were excluded due to assessing paediatric populations. There were a total of 11 studies that met the final inclusion criteria. An additional two case reports that met the criteria were identified by manuscript reviewers' comments. Thus, the total of 13 studies incorporated in this review included two systematic reviews, one retrospective cohort study, one retrospective chart review, two cross-sectional studies, one survey, and six case reports. The full search strategy and results are presented in Figure 1 and Table 1. The Cochrane Risk of Bias in Non-Randomized Studies – of Interventions [ROBINS-I] was used to assess the risk of bias in non-randomized studies presented in Table 2 [16].

All included studies, with the exception of the survey, reported at least one GIT symptom experienced in adult cannabis users. Reported GIT symptoms included nausea, vomiting, diarrhoea, abdominal pain/distension, constipation, loss of appetite, dehydration, adult intussusception (AI), and weight loss [8, 10, 17–27]. The severity of the symptoms varied, ranging from mild occurrences to requiring emergency

Table 1. Literature search on cannabis-induced gastrointestinal symptoms in the adult population

Study	Study design	Age group	Population	Recreational or medicinal use	Type of GI symptom experienced	Conclusions
Wang et al. [9] 2008	Systematic review	18 years or older	31 studies (23 RCTs and 8 observational studies)	Medicinal use	Vomiting Diarrhoea	Intensive vomiting and persistent diarrhoea are the most prevalent side effects associated to medical use of cannabis
Souza et al. [17] 2022	Systematic review	Various	12 RCTs (745 subjects, of which 454 used CBD)	Medicinal use	Diarrhoea, nausea, vomiting, abdominal pain/distention, constipation, loss of appetite	The most common side effects included GIT symptoms: (59.5%), somnolence (16.7%), loss of appetite (16.5%), and hypertransaminasemia (ALT/AST) (12.8%)
Lewis et al. [18] 2021	Retrospective cohort study	15–84 years old	1,214 subjects (456 with CHS, 758 with cannabis intoxication)	Chronic recreational use	Nausea, vomiting, abdominal pain, dehydration; all requiring ED admission	Of those with CHS, 98.2% had the chief complaint of nausea/vomiting compared to 16.9% with cannabis intoxication ($p < 0.001$), 87.7% of CHS patients had abdominal pain compared to 6.9% of those with cannabis intoxication ($p < 0.001$), and 39.3% of CHS patients had dehydration compared to 4% of those with cannabis intoxication ($p < 0.001$). Those with CHS had a longer duration of symptoms and length of ED stay ($p < 0.001$)
Soriano-Co et al. [19] 2010	Retrospective chart review	26–38 years old	8 subjects	Chronic recreational use	Nausea, vomiting (with and without blood), abdominal pain	All patients had a prodromal disorder characterised by abdominal discomfort and nausea, without vomiting, followed by an active phase, characterised by persistence of these prodromal symptoms and development of severe, persistent vomiting. All 6 patients had only minimal-to-mild distal oesophagitis or mild gastritis

Table 1 (continued)

Study	Study design	Age group	Population	Recreational or medicinal use	Type of GI symptom experienced	Conclusions
Patel et al. [20] 2019	Cross-sectional study	15–54 years old	55,549 subjects with a diagnosis of persistent vomiting (PV)	Unspecified	Persistent vomiting (PV)	The number of PV-related hospitalizations with cannabis use disorder (CUD) had a significantly increased trend ($p < 0.001$), with a 286% increase over 5 years. Regression analysis showed that cannabis use was associated with seven-fold higher odds (95% confidence interval: 6.931–7.260) of PV-related hospitalisation
Vanderziel and Alshaarawy [8] 2023	Cross-sectional study	20–59 years old	18,753 subjects (8,556 never users, 7,431 former users, 2,766 recent users)	Unspecified	Recent GIT illness defined as experiencing GIT illness with vomiting or diarrhoea that started in the 30 days prior to being surveyed	Compared to never users, frequent cannabis users were more likely to have higher prevalence of GIT illness ($p < 0.01$). Similar findings were observed when comparing infrequent or occasional cannabis users versus never users
Reynolds et al. [21] 2018	Survey	65 and older	345 subjects (32% reporting use at least once in their lifetime, 16% current users)	Recreational and medicinal	N/A	16% of respondents felt that they had experienced a side effect attributable to marijuana; 66% reported no adverse effects. 5 respondents described adverse effects they had experienced which did not include GIT effects
Yeoun et al. [22] 2020	Case report	54 years old (female)	1 subject	Chronic recreational use	Diffuse, cramping abdominal pain due to adult intussusception (AI)	Patient has no underlying medical issues; all tests were negative except urine toxicology which was cannabinoid positive several times. CT of the abdomen revealed a long-segment ileocolonic intussusception for which she received a right hemicolectomy

Table 1 (continued)

Study	Study design	Age group	Population	Recreational or medicinal use	Type of GI symptom experienced	Conclusions
Kothadia et al. [23] 2022	Case report	27–36 years old	4 subjects	Chronic recreational use	Severe abdominal pain, nausea, vomiting, diarrhoea, hematochezia due to AI	All subjects were long-term cannabis users presenting with similar GIT symptoms. Cannabis is thought to decrease GIT motility by inhibiting cholinergic mechanisms, predicted to be the cause of AI in these patients
Kakish et al. [24] 2020	Case report	18–38 years old	11 subjects	Chronic recreational use	Diffuse abdominal pain, vomiting due to AI	All 11 patients presented with GIT symptoms of an acute abdomen due to AI and none were found to have a pathologic process leading to an intussusception lead point. All 11 patients were cannabis users
Zaidi et al. [26] 2020	Case report	22 years old (female)	1 subject	Chronic recreational use	Sudden onset of progressive severe abdominal pain associated with nausea, episodes of non-bloody, non-bilious emesis, and dark-coloured loose stools due to AI	CT of the abdomen revealed small bowel intussusception in the left hemiabdomen, along with periportal oedema, with identifiable lead points for intussusception. Authors predict chronic cannabis use to be likely aetiology
Prokopchuk et al. [27] 2019	Case report	30 years old (male)	1 subject	Chronic recreational use	Admitted to the emergency department with a 24 h history of severe abdominal pain, diarrhoea and vomiting	CT of the abdomen showed several small bowel intussusceptions in the left abdominal region with diagnostic laparoscopy showing numerous, at least ten, regions of jejuno-jejunal intussusceptions
Bertolino et al. [25] 2014	Case report	29–46 years old	6 subjects	Chronic recreational use	Nausea, vomiting, abdominal pain, weight loss	Chronic cannabis use led to the clinical diagnosis of CHS in all 6 adults

department admission. Those with AI experienced additional symptoms such as diffuse cramping, hematochezia, and loose stools [24–27]. The survey conducted by Reynolds and colleagues [21] looked at recreational and medicinal cannabis use in the geriatric population (65 years and older) in Colorado. More than half of current users were aged 75 and older, and one-

quarter were aged 85 and older. Targeted symptoms for cannabis use were pain, sleep, anxiety, depression, appetite stimulation, headaches, GIT symptoms, glaucoma, PTSD, and seizures. Of the 345 participants surveyed, 32% had used cannabis at least once in their lifetime and 16% were current users at the time. Only 16% of respondents felt that they had experienced a side

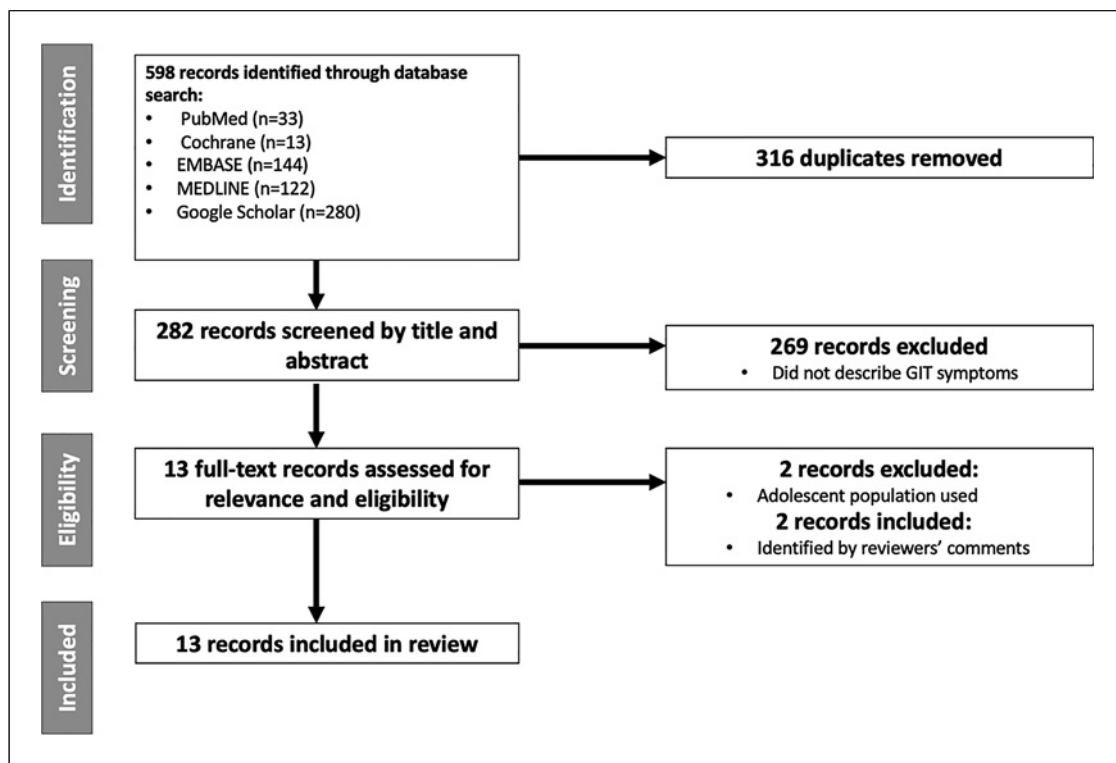


Fig. 1. PRISMA flowchart of search history.

Table 2. Risk of bias in non-randomized interventional studies using the ROBINS-I tool [32]

Study	Pre-intervention bias due to confounding	Bias in selection of participants into the study	At intervention bias in classification of interventions	Post-intervention bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results
Lewis et al. [18] 2021	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
Soriano-Co et al. [19] 2010	Moderate	Low	Low	Low	Low	Low	Moderate

effect attributable to marijuana, 5 of those respondents described the adverse effects they had experienced in further detail, which did not include GIT effects [21].

Vomiting and CHS

The most commonly reported GIT symptom was vomiting, observed in nine out of ten studies that reported GIT symptoms. Medically, cannabis is often used to prevent nausea and vomiting associated with chemo-

therapy. These antiemetic effects are thought to be due to the binding of THC, the psychoactive compound of cannabis, to cannabinoid receptors, prominently CB1, centrally and peripherally [28]. Research is still ongoing regarding the exact mechanism of vomiting induced by cannabis; however, there are proposed mechanisms for these paradoxical effects of cannabis on vomiting. It is posited that some individuals may be genetically predisposed to exhibit downregulation of CB1 after chronic

cannabis use [28, 29]. The presence of CB1 receptors in the GIT has shown to affect gastric motility in past studies, causing a significant delay in gastric emptying, potentially leading to vomiting [30]. A systematic review by Wang and colleagues [9] analysing 23 randomised clinical trials (RCTs) and eight observational studies, looked at adverse events related to medical use of cannabis and found that GIT adverse events were one of the highest experiences in this population of chronic cannabis users, at 16.5% compared to 6.7% in controls. Vomiting and diarrhoea were the most common. Another systematic review examining medical use of CBD therapy in 12 RCTs found that the most common side effects included gastrointestinal symptoms (59.5%), somnolence (16.7%), loss of appetite (16.5%), and hypertransaminasemia (ALT/AST) (12.8%) with statistical analysis revealing significance ($p \leq 0.05$) in using CBD for the increase in gastrointestinal symptoms, ALT/AST, rash, as well as change in appetite [17]. It should be noted that in Wang and colleagues [9] review, although GIT symptoms were the highest overall, there was no difference found in incidence of serious adverse events associated with medical cannabis use, but the rate of mild to moderate adverse events was 1.86 times higher in medical cannabis users. However, 99% of the side effects were reported from only two trials which highlight the severe lack of current research on long-term cannabis use overall.

A cross-sectional study looking at 18,753 subjects (8,556 never users, 7,431 former users, 2,766 recent users) found that compared to never users, frequent cannabis users were more likely to have higher prevalence of GIT illness ($p < 0.01$) [8]. Similar findings were observed when comparing infrequent or occasional cannabis users versus never users. GIT illness was defined as experiencing GIT symptoms associated with vomiting or diarrhoea that started in the 30 days prior to being surveyed. Another cross-sectional study examined 55,546 individuals with a diagnosis of persistent vomiting (PV) and found that cannabis use was associated with seven-fold higher odds of PV-related hospitalisation [20]. In addition, the number of PV-related hospitalizations with cannabis use disorder (CUD) had a significantly increased trend ($p < 0.001$), with a 286% increase over 5 years. Of note, the age range of this study was 15–54-year-old patients, and due to the retrospective nature of the study, there was no information on dose and duration of cannabis use.

Two of the included studies examined CHS [18, 25]. Chronic cannabis use has recently been shown to be associated with a pattern of nausea and vomiting de-

scribed as CHS [10]. CHS was first described in 2004 by Allen and colleagues [10] in individuals with heavy cannabis use. The ROME IV criteria are used to diagnose CHS clinically, which is defined as prolonged excessive cannabis use leading to episodic vomiting for greater than 6 months, which is relieved by sustained cessation of cannabis [31]. A retrospective cohort study by Lewis and colleagues [18] analysed 1,214 subjects (456 with CHS, 758 with cannabis intoxication) engaging in chronic recreational cannabis use and found that of those with CHS, 98.2% had the chief complaint of nausea/vomiting compared to 16.9% with cannabis intoxication ($p < 0.001$), 87.7% of CHS patients had abdominal pain compared to 6.9% of those with cannabis intoxication ($p < 0.001$), and 39.3% of CHS patients had dehydration compared to 4% of those with cannabis intoxication ($p < 0.001$) [18]. Additionally, those with CHS had a longer duration of symptoms and length of ED stay ($p < 0.001$). It must be noted that the diagnosis of CHS in this study was based on hospital discharge records and not established criteria and thus may differ. Additionally, cannabis use was self-reported. A case report on 6 chronic recreational users of cannabis showed that chronic cannabis use led to the clinical diagnosis of CHS in all six adults [25]. The users were three women and three men, presenting features that are typical of CHS; nausea, vomiting, abdominal pain, and weight loss. All medical investigations turned up negative, and their symptoms were improved by taking repeated hot showers. However, after addictions counselling and termination of cannabis use, the digestive symptoms ceased. Despite the emerging cases of CHS, research on the subject remains limited with small sample sizes and mostly anecdotal evidence, highlighting the need for further investigations.

Adult Intussusception

Intussusception refers to the invagination of a proximal portion of the bowel onto an adjacent distal segment and commonly occurs in paediatric populations, rarely adults [32]. Most cases of AI that do occur are due to neoplasms, strictures, post-operative adhesions, and endometriosis. Common symptoms include cramping abdominal pain, nausea, and vomiting [33]. If serious complications occur, obstruction and perforation leading to bloody diarrhoea and peritonitis can present as well. Computed tomography (CT) of the abdomen is the standard for confirming a diagnosis [32]. The mechanism of cannabis-induced AI is proposed to be due to activation of cannabinoid receptors in the GIT [4, 34]. CB1 receptors are located in the myenteric and

submucosal neurons of the GI tract, while CB2 receptors are located primarily on inflammatory and epithelial cells. It is thought that the activation of these receptors results in inhibition of acetylcholine release in presynaptic neurons leading to slowed contractile activity and peristalsis. Research has also shown that chronic cannabis use causes delayed gastric emptying [4]. It is hypothesised that this inhibition of peristalsis serves as a lead point for invagination leading to intussusception.

We found five case reports describing an association between cannabis use and AI [22–24]. A case report by Kothadia and colleagues [23] presented the cases of four individuals aged 27–36 years old presenting with similar GIT symptoms of severe abdominal pain, nausea, vomiting, diarrhoea, hematochezia due to AI. All patients were confirmed AI via CT scan and three were treated conservatively with substance cessation counselling, while one, a 27-year-old male using up to 2–3 g of cannabis per day for the past 10 years has had his jejunum surgically straightened [23]. A recent case series looking at 11 patients who presented with an acute abdomen over a 2-year period found that all 11 were diagnosed with small bowel AI on CT imaging [24]. None of the patients were found to have another pathologic process leading to an intussusception lead point; however, all were cannabis users. All cases were jejuno-jejunal intussusception, and 2 patients had more than one intussuscepted segment. Of these, one needed surgical intervention. Similarly, Yeoun and colleagues [22] described the case of a 54-year-old woman, a chronic recreational cannabis user, who experienced diffuse cramping and abdominal pain. She had no underlying medical issues, and all medical tests were negative except urine toxicology which was cannabinoid positive several times. CT of the abdomen revealed a long-segment ileocolic intussusception for which she received a right hemicolectomy. Similarly, case reports by Zaidi et al. [26], and Prokopchuk et al. [27] described the cases of a 22-year-old female and 30-year-old male, respectively, experiencing similar symptoms and CT findings, details of which are in Table 1.

Discussion

The aim of this systematic review was to comprehensively evaluate the GIT side effects induced by cannabis use. By synthesising and analysing the available evidence, this review identified several findings that can potentially contribute to our understanding of the impact of cannabis on gastrointestinal health in the adult population. All included studies, with the exception of the

survey, reported some type of GIT symptoms experienced in cannabis users ranging from nausea, vomiting, diarrhoea, abdominal pain, to AI [8, 10, 17–27].

Our analysis revealed that cannabis use is associated with a range of GIT side effects. The most commonly reported symptom is vomiting, followed by nausea, which was observed in multiple studies in both medical and recreational cannabis users. The mechanisms underlying cannabis-induced nausea and vomiting are not yet fully understood, but it has been proposed that activation of cannabinoid receptors in the brainstem may play a role [35]. Future research should aim to elucidate the underlying mechanisms and explore potential therapeutic interventions for these symptoms. Vomiting in the context of CHS is also of great clinical significance, given the severity of the symptoms that individuals face, the burden of care on the healthcare system, the scarcity of resources in terms of management and treatment. Abdominal pain was also reported in seven of the included studies, which is consistent with previous research suggesting that cannabis can affect gastrointestinal motility and lead to alterations in bowel habits [16–18, 21–24]. The case reports/series depicted cases of AI in cannabis users, with no other known causes to be found, although these data are strictly anecdotal in nature [22–24].

The findings of this review raise important considerations regarding the use of cannabis for medical purposes. While cannabis and cannabinoids are increasingly showing promise in the management of neuropathic pain, multiple sclerosis (MS), certain gastrointestinal disorders and chemotherapy induced nausea and vomiting, the potential for adverse effects cannot be ignored. As highlighted in this review, chronic usage of cannabis seems to be associated with an increased risk of GIT adverse effects and CHS. It is thus important to consider potential long-term effects of patients being prescribed cannabis for long-term alleviation of other medical conditions, as overtime they will become chronic users. Healthcare providers should be aware of the potential GIT side effects associated with cannabis use, not only when prescribing or recommending its use as a therapeutic option, but also in recreational users.

Limitations

It is important to acknowledge some limitations of this systematic review. Firstly, the available literature on cannabis-induced GIT side effects is relatively limited, and many studies have small sample sizes and short follow-up periods. Only two systematic reviews [9, 17]

utilizing RCT derived data on cannabis-induced adverse GIT effects were identified and were subject to the risk of bias found in Table 2. This limits the generalizability of the findings and highlights the need for larger, well-designed studies in this field, notably in the form of randomised clinical trials. Additionally, the majority of the studies included in this review were observational in nature, which prevents us from establishing causality. The research methodologies of the included studies varied significantly, with dosing and duration of cannabis use of different ranges, and unclear proportion of THC versus CBD. Additionally, there is a limited number of data available for specific at-risk populations, for example, geriatric cannabis use and resultant GIT effects. Only one study, the survey by Reynolds and colleagues [21], analysed cannabis use in the geriatric population. Due to limited available evidence of varying quality, definite conclusions were challenging to derive. While limited, evidence shows that the use of cannabis by geriatric populations is increasing. In the USA, it increased from 0.4% in 2006 and 2007 to 2.9% in 2015 and 2016 [36]. From 2016 to 2018, it further increased from 2.4% to 4.2%. This is relevant as geriatric cannabis use may be associated with increased mental health issues, substance use, and acute healthcare use [37]. GIT effects of cannabis use in the geriatric population include age-related digestive system changes (decreased motility, decreased gastric acid secretion), impact on bowel habits, and risk of nausea and vomiting. This is particularly concerning for older adults, leading to dehydration and electrolyte imbalances which can have more severe consequences.

Further Research

With increased prevalence of cannabis use worldwide, and recent legalisation in various areas, further research is warranted to garner a comprehensive understanding of cannabis effects on the human body, positive and negative. Specific attention must be paid to the beneficial and detrimental effects of long-term use of cannabis. RCTs with larger sample sizes, specified parameters, and appropriate long-term follow-ups are necessary. Further work should focus on understanding the potentially biphasic effect of cannabis on emesis, and thus the optimal dosing to prevent hyperemesis in long-term or high-dose users. The diagnosis of CHS must be further explored and education provided to healthcare workers, as it is likely underreported and thus under treated in emergency departments. Due to a lack of understanding of CHS, it can be a stigmatising diagnosis for individuals,

leading to withholding symptomatic care and treatment by providers [38]. The burden of care with CHS and GIT symptoms of cannabis on the adult population is high, and affects patient families and the entire healthcare system, thus research efforts on a global scale are required. Future research should focus on different populations, including geriatric, as clinical recognition and management will differ in age groups and possibly sex. Additionally, polypharmacy is an increasing concern in geriatric populations, and interactions of various medications with cannabis and their adverse GIT effects require further investigation.

Conclusions

The use of various forms of cannabinoids is widespread in the management of numerous medical ailments currently. However, with this associated use, adverse effects have been reported, especially pertaining to the gastrointestinal system in adults. This review reports specific GIT symptoms such as vomiting and AI that are experienced in adult cannabis users, highlighting their variety and severity. It alerts to the juxtaposing nature of cannabis utilization, in that it may alleviate symptoms in some users but conversely leads to adverse health outcomes in others. This review provides an opportunity for enhancement of further knowledge and contributes to the advancement of healthcare delivery by synthesising reported cases of gastrointestinal adverse effects (beyond nausea and vomiting) attributed to cannabis use, thereby providing healthcare professionals with up-to-date data, crucial in improving the management of patients and leading to safe prescribing practices. The lack of data available in vulnerable populations such as the geriatric population is also highlighted, stressing the importance for further research as geriatric cannabis use and adverse effects are likely underreported as this population is usually excluded from studies. These findings have important implications in knowledge translation for the management of symptoms in both recreational and medical cannabis users. Further research will enable healthcare providers to educate the public on the safe use of cannabinoid containing products. It may also provide policymakers with valuable information on the potential health risks associated with cannabis use and can lead to the development of enhanced public health policies promoting safe and responsible cannabis use. This review emphasises the importance of a balanced assessment of the risks and benefits of cannabis use, particularly with regard to gastrointestinal health in the adult population, and alerts to the need for the inclusion and close attention to frail geriatric populations.

Statement of Ethics

Ethics approval was not required for this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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References

- 1 United Nations: Office on Drugs and Crime. World Drug Report 2022. 2022 [cited 2023 May 28]. Available from: <https://www.unodc.org/unodc/en/data-and-analysis/world-drug-report-2022.html>.
- 2 NCCIH. Cannabis (Marijuana) and Cannabinoids: What you need to know. 2019 [cited 2023 May 28]. Available from: <https://www.nccih.nih.gov/health/cannabis-marijuana-and-cannabinoids-what-you-need-to-know>.
- 3 Pertwee RG. Endocannabinoids and their pharmacological actions. *Handb Exp Pharmacol*. 2015;231:1–37.
- 4 Pertwee RG. Cannabinoids and the gastrointestinal tract. *Gut*. 2001;48(6):859–67.
- 5 Intiaz S, Wells S, Rehm J, Hamilton HA, Nigatu YT, Wickens CM, et al. Cannabis use during the COVID-19 pandemic in Canada: a repeated cross-sectional study. *J Addict Med*. 2021;15(6):484–90.
- 6 Cohen K, Weizman A, Weinstein A. Positive and negative effects of cannabis and cannabinoids on health. *Clin Pharmacol Ther*. 2019;105(5):1139–47.
- 7 Campeny E, López-Pelayo H, Nutt D, Bli-thikioti C, Oliveras C, Nuño L, et al. The blind men and the elephant: systematic review of systematic reviews of cannabis use related health harms. *Eur Neuropsychopharmacol*. 2020;33:1–35.
- 8 Vanderziel A, Alshaarawy O. Cannabis use and gastrointestinal tract illnesses: the national health and nutrition examination surveys, 2005–2018. *Drug Alcohol Rev*. 2023; 42(4):785–90.
- 9 Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systematic review. *CMAJ*. 2008;178(13):1669–78.
- 10 Allen JH, de Moore GM, Heddle R, Twartz JC. Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. *Gut*. 2004;53(11):1566–70.
- 11 Shah J, Fermo O. Review of systemic and syndromic complications of cannabis use: a review. *Medicine*. 2022;101(49):32111.

Author Contributions

Helen Senderovich: conception, design, drafting, clinical revisions, and approval of final version. Christopher Meaney: drafting of the paper and interpretation of the data. Srishti Vashishtha: drafting of the paper, interpretation of the data, and critical revisions of the paper.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

- 12 Kichloo A, Albosta M, Aljadah M, El-Amir Z, Goldar G, Khan MZ, et al. Marijuana: a systems-based primer of adverse effects associated with use and an overview of its therapeutic utility. *SAGE Open Med*. 2021;9: 205031212110009.
- 13 Canada H. Product information [cited 2023 Oct 22]. Available from: <https://health-products.canada.ca/dpd-bdpp/info?lang=eng&code=75157>.
- 14 EPIDIOLEXhcp.com [Internet]. [cited 2023 Oct 23]. Forms and Downloads | EPIDIOLEX® (cannabidiol). Available from: <https://www.epidioxhcp.com/resources/forms-and-downloads>.
- 15 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:2535.
- 16 Sterne J, Hernan M, Reeves B, Savovic J, Berkman N, Viswanathan M. Risk of bias tools - ROBINS-I detailed guidance; 2016. [cited 2023 Jul 1]. Available from: <https://www.riskofbias.info/>.
- 17 Souza JDR, Pacheco JC, Rossi GN, de-Paulo BO, Zuardi AW, Guimaraes FS, et al. Adverse effects of oral cannabidiol: an updated systematic review of randomized controlled trials (2020–2022). *Pharmaceutics*. 2022; 14(12):2598.
- 18 Lewis B, Leach E, Fomum Mugri LB, Keung MY, Ouellette L, Riley B, et al. Community-based study of cannabis hyperemesis syndrome. *Am J Emerg Med*. 2021;45:504–5.
- 19 Soriano-Co M, Batke M, Cappell MS. The cannabis hyperemesis syndrome characterized by persistent nausea and vomiting, abdominal pain, and compulsive bathing associated with chronic marijuana use: a report of eight cases in the United States. *Dig Dis Sci*. 2010;55(11):3113–9.
- 20 Patel RS, Patel J, Jaladi PR, Bhimanadham NN, Imran S, Tankersley WE. Burden of persistent vomiting with cannabis use disorder: report from 55,549 hospitalizations in

- the United States. *Psychosomatics*. 2019; 60(6):549–55.
- 21 Reynolds IR, Fixen DR, Parnes BL, Lum HD, Shanbhag P, Church S, et al. Characteristics and patterns of marijuana use in community-dwelling older adults. *J Am Geriatr Soc*. 2018; 66(11):2167–71.
- 22 Yeoun D, El Younis C, Ali Y, Ahmed MF. S1692 chronic cannabis user presenting with intussusception: a diagnostic challenge and preventive implications. *Am J Gastroenterol*. 2020;115(1):S870–1.
- 23 Kothadia JP, Dash A, Verma R, Kreitman K, Snell PD, Ismail MK. Adult intussusception in chronic marijuana users. *Gastroenterol Res*. 2022;15(5):278–83.
- 24 Kakish D, Alaoudi M, Welch B, Fan D, Meghpara M, Mandava N, et al. Small bowel intussusception in marijuana users. *J Surg Case Rep*. 2020;2020(9):335.
- 25 Bertolino J, Abdo L, Khau D, Meckenstock R, Sautereau N, Jean E, et al. [Cannabinoid hyperemesis syndrome: about 6 cases]. *Rev Med Interne*. 2015;36(10):694–7.
- 26 Zaidi SR, Khan ZH, Mukhtar K, Ahmed MM, Syed SH. A case of intussusception in a patient with marijuana use: coincidence or possible correlation? *Cureus*. 2020;12(3): 7493.
- 27 Prokopchuk O, Neumann PA, Hüser N, Friess H, Wilhelm D. Multiple intestinal intussusceptions caused by highly impaired gastrointestinal motility in a patient with chronic cannabis consumption. *J Surg Case Rep*. 2019;2019(5):160.
- 28 Darmani NA, Ray AP. Evidence for a re-evaluation of the neurochemical and anatomical bases of chemotherapy-induced vomiting. *Chem Rev*. 2009;109(7):3158–99.
- 29 Romero J, Berrendero F, Manzanares J, Pérez A, Corchero J, Fuentes JA, et al. Time-course of the cannabinoid receptor down-regulation in the adult rat brain caused by repeated exposure to delta9-tetrahydrocannabinol. *Synapse*. 1998;30(3):298–308.

- 30 McCallum RW, Soykan I, Sridhar KR, Ricci DA, Lange RC, Plankey MW. Delta-9-tetrahydrocannabinol delays the gastric emptying of solid food in humans: a double-blind, randomized study. *Aliment Pharmacol Ther.* 1999;13(1):77–80.
- 31 Drossman DA, Hasler WL. Rome IV-functional GI disorders: disorders of gut-brain interaction. *Gastroenterology.* 2016;150(6):1257–61.
- 32 Marinis A, Yiallourou A, Samanides L, Dafnios N, Anastasopoulos G, Vassiliou I, et al. Intussusception of the bowel in adults: a review. *World J Gastroenterol.* 2009;15(4):407–11.
- 33 Huang BY, Warshauer DM. Adult intussusception: diagnosis and clinical relevance. *Radiol Clin North Am.* 2003;41(6):1137–51.
- 34 Wright KL, Duncan M, Sharkey KA. Cannabinoid CB2 receptors in the gastrointestinal tract: a regulatory system in states of inflammation. *Br J Pharmacol.* 2008;153(2):263–70.
- 35 Kendall DA, Yudowski GA. Cannabinoid receptors in the central nervous system: their signaling and roles in disease. *Front Cell Neurosci.* 2016;10:294.
- 36 Han BH, Palamar JJ. Trends in cannabis use among older adults in the United States, 2015-2018. *JAMA Intern Med.* 2020;180(4):609–11.
- 37 Wolfe D, Corace K, Butler C, Rice D, Skidmore B, Patel Y, et al. Impacts of medical and non-medical cannabis on the health of older adults: findings from a scoping review of the literature. *PLoS One.* 2023;18(2):e0281826.
- 38 Jensen AD. Challenges with acute care and response to treatment among adult patients with cyclic vomiting syndrome. *Gastroenterol Nurs.* 2015;38(6):469–76.