Cannabinoid Use in Patients With Gastroparesis and Related Disorders: Prevalence and Benefit

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OBJECTIVES: **Gastroparesis (Gp) can be a challenging disorder to manage due to the paucity of treatment options. We do not know how frequently patients with Gp symptoms resort to cannabinoids to address their symptoms. This study (i) determines the prevalence of cannabinoid use in patients with Gp symptoms, (ii) describes the patients with Gp symptoms using cannabinoids, and (iii) assesses the patients' perceived benefit of cannabinoids for Gp symptoms.**

METHODS: **Consecutive outpatients with symptoms suggestive of Gp seen on follow-up at our academic center from June 2018 to September 2018 filled out questionnaires on their symptoms and the current treatments.**

RESULTS: **Of 197 patients, nearly half (n = 92, 46.7%) reported current (35.5%) or past (11.2%) use of cannabinoids, including tetrahydrocannabinol (n = 63), dronabinol (n = 36), and/or cannabidiol (n = 16). Of these, most perceived improvement in Gp symptoms from cannabinoids (93.5% with tetrahydrocannabinol, 81.3% with cannabidiol, and 47.2% with dronabinol). Cannabinoids were used most commonly via smoking (n = 46). Patients taking cannabinoids were younger (41.0 ± 15.4 vs 48.0 ± 15.9 years; $P < 0.01$) and had a higher Gastroparesis Cardinal Symptom Index total score (3.4 ± 1.0 vs 2.8 ± 1.3; $P < 0.01$) compared with patients with no history of cannabinoid use.**

CONCLUSIONS: **A third of patients with Gp symptoms actively use cannabinoids for their chronic symptoms. Most of these patients perceive improvement in their symptoms with cannabinoids. Patients taking cannabinoids were younger and more symptomatic than those not taking cannabinoids. Further studies on the efficacy and safety of cannabinoids in Gp will be useful.**

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INTRODUCTION

Gastroparesis (Gp) is a syndrome of delayed gastric emptying in the absence of mechanical obstruction (1). The symptoms of Gp include nausea, vomiting, early satiety, postprandial fullness, abdominal discomfort, and lack of appetite. These symptoms frequently impair the quality of lives of the affected individuals. Gp is often treated with dietary modifications, prokinetic agents to accelerate gastric emptying, and antiemetic agents to decrease nausea and vomiting. For refractory cases, feeding tubes, gastric electric stimulator, and/or pyloromyotomy may be considered. A third of patients with Gp express dissatisfaction with the available treatment options (2). We do not know how often patients with symptoms of Gp resort to complementary and alternative treatments, including cannabinoids, to address their chronic symptoms.

Cannabinoids are a group of compounds that act on cannabinoid receptors; these include plant-derived cannabinoids (phytocannabinoids), synthetic cannabinoids, and endogenously derived cannabinoids (endocannabinoids) (3). The natural cannabinoid plant *Cannabis sativa* has been cultivated by humans worldwide for many years for medicinal and recreational purposes. Natural and synthetic cannabinoids are being increasingly used in the United States, especially in states that have decriminalized *Cannabis* use (4). A US population-based online survey in 2017 showed that 14.6% of the US adults used marijuana in the last year (5). There is some evidence for cannabinoids in helping treat patients with chronic pain and chemotherapy-induced nausea and vomiting (6). Cannabinoids may have therapeutic potential in patients with gastrointestinal (GI) disorders, including inflammatory bowel disease (IBD) (7). In Pennsylvania, the use of medical marijuana was legalized in 2016 for several medical conditions including IBD, severe chronic pain (seen in some patients with Gp), neuropathies (frequently present in patients with diabetic Gp), and some neurologic disorders that can secondarily delay gastric emptying (such as Parkinson's disease and multiple sclerosis).

The main ingredients in *Cannabis* are tetrahydrocannabinol (THC)—the psychoactive component of marijuana—and

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cannabidiol (CBD)—the nonpsychoactive component. THC and CBD activate 2 endogenous cannabinoid receptors: CB1 and CB2 receptors (4). CB1 receptors are present throughout the GI tract, mainly in the myenteric and submucosal neurons, and also in the epithelial cells (8). CB1 receptor agonists inhibit GI peristalsis through the inhibition of excitatory acetylcholine in the presynaptic neurons (9). By contrast, CB2 receptors are predominantly located on the inflammatory and epithelial cells and to a lesser degree on the myenteric and submucosal neurons (10,11). Dronabinol, a synthetic cannabinoid medicine, is a nonselective cannabinoid receptor agonist (4). It is approved for chemotherapy-induced nausea and vomiting and for anorexia in patients with acquired immune deficiency syndrome. It is used off label in some patients with severe symptoms of Gp, particularly anorexia and nausea.

There are no studies on the prevalence of cannabinoid use in patients with symptoms of Gp. The characteristics of patients with symptoms of Gp using cannabinoids and the perceived benefit of cannabinoids for their symptoms are also not known. The primary aims of this study are to (i) determine the prevalence of cannabinoid use in patients with Gp symptoms, (ii) describe the patients with Gp symptoms using cannabinoids, and (iii) assess the patients' perceived benefit of cannabinoids for Gp symptoms. We also wanted to determine the prevalence and perceived benefit of other alternative or complementary treatments of Gp symptoms.

METHODS

Consecutive patients seen on follow-up at Temple University Hospital Motility Center with symptoms suggestive of Gp (chronic nausea, vomiting, early satiety, and/or postprandial fullness) from June 2018 to September 2018 were studied. This study was reviewed and approved by the Temple University Hospital Institutional Review Board. Patients are often referred to our tertiary care center for persistent or refractory symptoms of Gp. Subjects were recruited at the end of their regularly scheduled appointments after obtaining informed consent. Patients were explained that the aims of this study were to determine the prevalence and perceived benefit of complementary and alternative treatments in patients with symptoms suggestive of Gp and the characteristics of the patients using these treatments. Inclusion criteria were the following: (i) adults aged 18 years or above and (ii) symptoms suggestive of Gp. Only patients seen on follow-up were included as they had a physician-patient relationship and, in our opinion, were more likely to be truthful about cannabinoid use. Despite the changing attitude toward *Cannabis*, its use even for therapeutic purposes may be considered stigmatizing (12). Hence, we did not include patients who were evaluated for the first time at our Motility Center, as these patients may have concealed information on cannabinoid use, possibly resulting in an underestimation of the prevalence of cannabinoid use in patients with symptoms suggestive of Gp.

Patients were asked to fill out questionnaires. These contained a questionnaire on alternative/complementary treatments, social history (alcohol use, smoking, use of hot showers for the relief of symptoms), and medication history (including anti-emetics and opioids). Patients also filled the Patient Assessment of Upper Gastrointestinal Symptoms (PAGI-SYM) and the Rome IV Diagnostic Questionnaires for functional dyspepsia and chronic nausea and vomiting syndrome (CNVS). We also asked patients to fill the Rome IV Diagnostic Questionnaire for cyclic vomiting syndrome (CVS) and cannabinoid hyperemesis syndrome (CHS) to make sure they did not meet the criteria for CVS or CHS. We retrospectively reviewed patients' demographics (age, gender, race), body mass index (BMI) recorded during their physical examination, results of the 4-hour gastric emptying scintigraphy (GES) previously performed as part of their clinical evaluation (13), and medical and surgical histories (including surgical treatments of Gp).

Questionnaire on alternative/complementary treatments

This questionnaire asked about taking alternative or complementary treatments of symptoms of Gp including cannabinoids, probiotics, herbal supplements, ginger, acupuncture, acupressure, hypnosis, massage therapy, and/or others. The patients taking cannabinoids provided additional information on the type of cannabinoid (including marijuana/THC, CBD, and dronabinol) and the form of cannabinoid (including smoke, vapor, edibles such as capsules, oils or foods, and transdermal). The patients also reported the duration, frequency, and reason for cannabinoid use. Those taking marijuana were asked whether this was medical marijuana. The patients who were taking alternative or complementary treatments reported the perceived benefit of these treatments on the symptoms of Gp using a 7-point Likert scale (completely better, considerably better, somewhat better, unchanged, somewhat worse, considerably worse, and very considerably worse).

PAGI-SYM

This validated questionnaire is for the upper GI symptoms of Gp, functional dyspepsia, and gastroesophageal reflux disease (14). Patients rated the severity of 22 common GI symptoms over the previous 2 weeks as none (0), very mild (1), mild (2), moderate (3), severe (4), and very severe (5). Gastroparesis Cardinal Symptom Index (GCSI) consists of 3 subscales of the PAGI-SYM to measure the important symptoms of Gp. The GCSI total score is calculated as the average of the following 3 symptom subscales: nausea/vomiting subscale (3 items: nausea, vomiting, and retching), postprandial fullness/early satiety subscale (4 items: stomach fullness, early satiety, postprandial fullness, and loss of appetite), and bloating subscale (2 items: bloating and stomach distension) (15). The PAGI-SYM has 3 additional subscales including upper abdominal pain subscale (2 items: upper abdominal pain and upper abdominal discomfort), lower abdominal pain subscale (2 items: lower abdominal pain and lower abdominal discomfort), and heartburn/regurgitation subscale (7 items: regurgitation/reflux during the day and on lying down, heartburn during the day and on lying down, chest discomfort during the day and at nighttime, and bitter/acid/sour taste in the mouth). Patients were also asked to rate the severity of constipation and diarrhea using the PAGI-SYM scale.

Rome IV Diagnostic Questionnaire

We used a modified brief version of the Rome IV Diagnostic Questionnaire (16), where the patients were asked to report the frequency of postprandial fullness, early satiety, upper abdominal pain/burning, nausea, and vomiting. The patients with symptom-duration of more than 6 months reported the frequency of their symptoms over the past 3 months using the Rome IV symptom frequency scale as one of the following: never, fewer than 1 day a month, 1 day a month, 2–3 days a month, 1 day a week, 2–3 days

Table 1. Characteristics of cannabinoid use (active use or history) in patients with Gp and related disorders

Characteristic	
Type of cannabinoids, n (%)	
Marijuana/THC	63 (68.5)
Dronabinol	36 (39.1)
CBD	16 (17.4)
Form of cannabinoids, n (%)	
Smoke	46 (50)
Pills	36 (39.1)
Oils	14 (15.2)
Vapor	13 (14.1)
Transdermal	4 (4.3)
Medical marijuana, n (%)	22 (23.9)
Reason for cannabinoid use, n (%)	
Nausea and vomiting	72 (78.3)
Abdominal pain	36 (39.1)
Loss of appetite	17 (20.7)
Anxiety	4 (4.3)
Migraine	3 (3.3)
Recreational use	3 (3.3)
Insomnia	2 (2.2)
Fibromyalgia	1 (1.1)
Neuropathy	1 (1.1)
Stress	1 (1.1)
Mean duration of cannabinoid use (mean ± s.d. in yr)	4.5 ± 6.7
% Patients using cannabinoid at least several times per week	82.4

This table includes patients who were actively using cannabinoids (n = 70) or reported a history of cannabinoid use (n = 22). Percentages were calculated from patients who reported current or past use of cannabinoids.
CBD, cannabidiol; Gp, gastroparesis; THC, tetrahydrocannabinol.

a week, most days, every day, or multiple times per day/all the time.

Patients meet the Rome IV diagnostic criteria for functional dyspepsia if they fulfill the criteria for postprandial distress syndrome and/or epigastric pain syndrome and do not have any evidence of structural disease to explain their symptoms (17). The Rome IV diagnostic criteria for postprandial distress syndrome include (i) bothersome postprandial fullness severe enough to affect the usual activities and/or (ii) bothersome early satiation severe enough to prevent finishing a regular-sized meal, lasting a total of at least 3 days per week that can be on separate days (17). Patients with bothersome epigastric pain or burning severe enough to affect the usual activities at least 1 day per week meet the Rome IV diagnostic criteria for epigastric pain syndrome (17). The Rome IV criteria for CNVS include all the following: (i) bothersome nausea severe enough to affect the usual activities at least 1 day per week and/or 1 more vomiting episode per week; (ii) self-induced vomiting, eating disorders, regurgitation, or rumination are excluded; and (iii) no evidence of organic, systemic, or metabolic diseases that can explain the symptoms (17). Patients with episodes of vomiting of acute onset and duration less than 1 week meet the Rome IV criteria for CVS if they have (i) at least 3 discrete episodes in the last year and 2 episodes in the last 6 months, occurring at least 1 week apart, and (ii) absence of vomiting between episodes, but other milder symptoms may be present (17). The Rome IV criteria for CHS include (i) episodic vomiting suggestive of CVS, (ii) onset of symptoms after prolonged excessive *Cannabis* use, and (iii) relief of vomiting episodes after sustained cessation of *Cannabis* (17).

Statistical analysis

The responses to the questionnaires were compiled in Microsoft Excel database. Student's *t* test was used for quantitative data. Mann-Whitney *U* test was used to compare symptoms recorded on the ordinal scale. These results are expressed as mean ± s.d. Chi-squared test was used for categorical data, with results expressed as percentages. *P* value of <0.05 was considered statistically significant. No adjustment for multiple comparisons was made. Missing answers were excluded from the analyses.

RESULTS

Of the 197 patients, 154 (78.2%) had delayed gastric emptying, including 64 patients with idiopathic Gp, 57 with diabetic Gp, 28 with atypical Gp (eating disorder = 12, hypothyroidism = 8, reflux sympathetic dystrophy = 5, lupus = 2, multiple sclerosis = 2, rheumatoid arthritis = 2, Sjogren's syndrome = 2, and scleroderma = 1), and 5 with postsurgical Gp (fundoplication = 4 and Roux-en-Y = 1). The remaining 43 patients (normal gastric emptying = 35, GES not available = 4, rapid gastric emptying = 2, and could not tolerate GES = 2) met the Rome IV criteria for CNVS (n = 38) and/or functional dyspepsia (n = 34).

Prevalence of cannabinoid use

Nearly half of all patients (n = 92, 46.7%) reported current or past use of cannabinoids (Table 1). The cannabinoids used by the patients included marijuana (n = 63), dronabinol (n = 36), and CBD (n = 16). Of all patients with current or past use of cannabinoids, 53 (57.6%) reported auto-prescribing cannabinoids (using cannabinoids on their own volition), including marijuana (n = 41) and/or CBD (n = 13), whereas 48 (52.2%) were recommended cannabinoids by healthcare providers, including dronabinol (n = 36), medical marijuana (n = 22), and/or medically prescribed CBD (n = 3). Nine patients gave a history of both volitional use and using medically prescribed cannabinoids. Mean duration of cannabinoid use was 4.5 ± 6.7 years. Most of these patients (n = 78) used cannabinoids at least several times per week, with 67 patients reporting daily use. Cannabinoids were used most commonly via smoking (n = 46), pills (n = 36), oils (n = 14), and vapors (n = 13). The most common reasons for cannabinoid use were relief of nausea and vomiting (n = 72), abdominal pain (n = 36), and loss of appetite (n = 17), with only one patient reporting using cannabinoids solely for recreational purposes. Over a third (n = 70, 35.5%) were actively taking cannabinoids, including marijuana (n = 49), dronabinol (n = 14), and/or CBD (n = 13).

Perceived benefit of cannabinoids

Most patients with Gp using cannabinoid perceived improvement in Gp symptoms from cannabinoids (Table 2). Among patients with active/past marijuana use (excluding one patient who used marijuana solely for recreational purposes), 93.5%

Table 2. Perceived benefit of cannabinoids and other alternative/complementary treatments in patients with Gp and related disorders

Factor	Better			Unchanged	Worse			No response
	Completely	Significantly	Somewhat		Somewhat	Considerably	Very considerably	
Cannabinoids								
Marijuana/THC (62 users)[a]	4 (6.5)	30 (48.4)	24 (38.7)	4 (6.5)	0 (0)	0 (0)	0 (0)	0 (0)
CBD (16 users)	0 (0)	4 (25)	9 (56.3)	3 (18.8)	0 (0)	0 (0)	0 (0)	0 (0)
Dronabinol (36 users)	0 (0)	7 (19.4)	10 (27.8)	11 (30.6)	1 (2.8)	0 (0)	0 (0)	7 (19.4)
Other alternative/complementary treatments								
Probiotics (81 users)	0 (0)	6 (7.4)	30 (37)	36 (44.4)	1 (1.2)	0 (0)	0 (0)	8 (9.9)
Ginger (56 users)	0 (0)	3 (5.4)	29 (51.8)	18 (32.1)	0 (0)	1 (1.8)	0 (0)	5 (8.9)
Acupuncture (30 users)	0 (0)	5 (16.7)	5 (16.7)	14 (46.7)	1 (3.3)	0 (0)	0 (0)	5 (16.7)
Herbal supplements (23 users)	0 (0)	2 (8.7)	7 (30.4)	9 (39.1)	1 (4.3)	0 (0)	0 (0)	4 (17.4)
Acupressure (8 users)	0 (0)	0 (0)	3 (37.5)	4 (50)	0 (0)	0 (0)	0 (0)	1 (12.5)
Massage (5 users)	0 (0)	0 (0)	2 (40)	2 (40)	0 (0)	0 (0)	0 (0)	1 (20)
Hypnosis (3 users)	0 (0)	0 (0)	0 (0)	2 (66.7)	0 (0)	0 (0)	0 (0)	1 (33.3)

This table includes patients who were actively using cannabinoids (n = 70) and/or other alternative/complementary treatments (n = 91), as well as patients who reported a history of cannabinoid (n = 22) and/or other alternative/complementary treatments use (n = 23). Other uncommonly used alternative/complementary treatments included chiropractor treatments (n = 2), apple cider vinegar (n = 1), holy basil (n = 1), melatonin (n = 1), peppermint oil (n = 1), and turmeric (n = 1). Values are expressed as n (%).
CBD, cannabidiol; GI, gastrointestinal; Gp, gastroparesis; THC, tetrahydrocannabinol.
[a]Excludes one other patient who reported taking marijuana solely for recreational purposes, did not report the impact of marijuana on GI symptoms; hence, the perceived benefit question was not applicable to this patient.

reported improvement in their symptoms with marijuana (6.5% completely better, 48.4% significantly better, and 38.7% somewhat better), with only 6.5% reporting unchanged symptoms and none reporting worsening of symptoms. Likewise, most patients (81.3%) with active/past CBD use had improvement in their Gp symptoms with CBD (25% significantly better and 56.3% somewhat better), with 18.8% reporting unchanged symptoms. Among 36 patients with current or past use of dronabinol, nearly half (47.2%) experienced improvement in symptoms (19.4% significantly better and 27.8% somewhat better). About a third of patients (30.6%) with dronabinol use had unchanged symptoms, 19.4% did not respond to the perceived benefit question, with one patient reporting somewhat worse nausea with dronabinol. Patients taking natural cannabinoids (THC and/or CBD) were more likely to report improvement in their symptoms of Gp compared with patients taking dronabinol (91% vs 47%; $P < 0.01$).

Severity of GI symptoms

Using the PAGI-SYM questionnaire, the patients with symptoms of Gp had a GCSI total score of 3.1 ± 1.2 (Table 3). We compared the severity of symptoms between patients actively taking cannabinoids (n = 70) and patients with no history of cannabinoid use (n = 105), excluding the patients with a history of cannabinoid use due to a small sample size of this subgroup (n = 22). Patients actively taking cannabinoids were more symptomatic with a higher GCSI total score compared with patients with no history of cannabinoid use (3.4 ± 1.0 vs 2.8 ± 1.3; $P < 0.01$). Cannabinoid-using patients scored higher than cannabinoid nonusers on nausea/vomiting subscale, postprandial fullness/early satiety subscale, upper abdominal pain subscale, and lower abdominal pain subscales ($P < 0.01$), with a trend to score higher on heartburn/regurgitation subscale ($P = 0.07$). There was no difference between cannabinoid users and nonusers on the bloating subscale.

Comparing the severity of individual symptoms, cannabinoid-using patients with symptoms of Gp had a higher severity of nausea, retching, vomiting, stomach fullness, early satiety, loss of appetite, upper abdominal pain, upper abdominal discomfort, lower abdominal pain, lower abdominal discomfort, chest discomfort during day, and chest discomfort at night compared with cannabinoid-naive patients with Gp symptoms. Among patients with active cannabinoid use, only a minority (n = 12, 17.1%) reported cannabinoid use before the onset of symptoms of Gp, whereas most (n = 57, 81.4%) started using cannabinoids after the onset of their Gp symptoms (one patient reported the same duration of cannabinoid use and Gp symptoms).

Gastric emptying and types of Gp

Among patients with symptoms of Gp actively using cannabinoids, 74.3% had delayed gastric emptying compared with 82.9% patients with no history of cannabinoid use ($P = 0.17$; Table 4). There were no differences between active cannabinoid users and cannabinoid-naive patients with respect to the 2- and 4-hour gastric retention on GES. Cannabinoid users and nonusers also did not differ in the prevalence of different subtypes of Gp.

Medication use and surgical treatments of Gp

Most patients (86.8%) in our study were using anti-emetics to help control their symptoms of Gp, and nearly a third (31%) reported opioid use (Table 4). A considerable minority of the patients had histories of surgical treatments for the management of their Gp symptoms including gastric stimulators (31.5%), feeding tubes (12.7%), and/or pyloromyotomy (5.6%). There were no differences between active cannabinoid users and patients with no history of

Table 3. Severity of symptoms on the PAGI-SYM Questionnaire in patients with Gp and related disorders, including patients actively on cannabinoids and patients with no history of cannabinoid use

Factor	All patients (N = 197)	Patients actively on cannabinoids (n = 70)	Patients with no history of cannabinoid use (n = 105)	*P* value
PAGI-SYM: individual symptoms				
Nausea	3.4 ± 1.5	3.8 ± 1.3	3.0 ± 1.6	**<0.01**
Retching	2.3 ± 1.7	2.6 ± 1.7	1.9 ± 1.7	**0.01**
Vomiting	2.1 ± 1.8	2.6 ± 1.8	1.7 ± 1.7	**<0.01**
Stomach fullness	3.7 ± 1.3	3.9 ± 1.3	3.5 ± 1.3	**0.02**
Early satiety	3.5 ± 1.5	3.8 ± 1.4	3.2 ± 1.6	**0.01**
Postprandial fullness	3.6 ± 1.5	3.7 ± 1.6	3.5 ± 1.5	0.16
Loss of appetite	3.2 ± 1.6	3.7 ± 1.4	2.7 ± 1.7	**<0.01**
Bloating	3.3 ± 1.6	3.4 ± 1.4	3.1 ± 1.7	0.22
Stomach or belly visibly larger	2.9 ± 1.7	3.1 ± 1.6	2.8 ± 1.7	0.30
Upper abdominal pain	3.0 ± 1.6	3.3 ± 1.7	2.6 ± 1.7	**<0.01**
Upper abdominal discomfort	3.1 ± 1.6	3.5 ± 1.5	2.7 ± 1.5	**<0.01**
Lower abdominal pain	2.4 ± 1.6	2.9 ± 1.6	2.1 ± 1.6	**<0.01**
Lower abdominal discomfort	2.5 ± 1.6	3.0 ± 1.5	2.1 ± 1.6	**<0.01**
Heartburn during the day	2.0 ± 1.7	2.2 ± 1.8	1.9 ± 1.6	0.33
Heartburn when lying down	2.1 ± 1.7	2.2 ± 1.7	2.0 ± 1.7	0.40
Feeling of discomfort inside chest during the day	1.7 ± 1.5	2.0 ± 1.6	1.4 ± 1.4	**0.01**
Feeling of discomfort inside chest at night	1.6 ± 1.6	1.9 ± 1.7	1.4 ± 1.5	**0.04**
Regurgitation or reflux during the day	2.1 ± 1.6	2.3 ± 1.7	1.9 ± 1.6	0.15
Regurgitation or reflux when lying down	2.1 ± 1.7	2.3 ± 1.7	1.8 ± 1.7	0.16
Bitter, acid, or sour taste in mouth	2.1 ± 1.7	2.3 ± 1.7	1.9 ± 1.6	0.12
Constipation	2.5 ± 1.8	2.3 ± 1.9	2.6 ± 1.7	0.28
Diarrhea	1.8 ± 1.8	2.0 ± 1.8	1.5 ± 1.7	0.07
PAGI-SYM subscales				
GCSI: total score	3.1 ± 1.2	3.4 ± 1.0	2.8 ± 1.3	**<0.01**
GCSI: nausea/vomiting subscale	2.6 ± 1.4	3.0 ± 1.3	2.2 ± 1.5	**<0.01**
GCSI: postprandial fullness/early satiety subscale	3.5 ± 1.3	3.8 ± 1.2	3.2 ± 1.3	**<0.01**
GCSI: bloating subscale	3.1 ± 1.6	3.2 ± 1.4	2.9 ± 1.7	0.24
Upper abdominal pain subscale	3.0 ± 1.8	3.4 ± 1.6	2.6 ± 1.6	**<0.01**
Lower abdominal pain subscale	2.5 ± 1.6	2.9 ± 1.5	2.1 ± 1.5	**<0.01**
Heartburn/regurgitation subscale	2.0 ± 1.4	2.2 ± 1.4	1.8 ± 1.3	0.08

Results are expressed as mean ± s.d. *P* value (calculated using Mann-Whitney *U* Test) compares patients actively using cannabinoids with patients with no history of cannabinoid use.
GCSI, Gastroparesis Cardinal Symptom Index; Gp, gastroparesis; PAGI-SYM, Patient Assessment of Gastrointestinal Symptoms.
Valued in bold are statistically significant.

cannabinoid use with respect to their current anti-emetic use, opioid use, or previous surgical treatments of Gp symptoms.

Demographics and social history

Mean age of the patients in this study was 44.9 ± 15.9 years. The patients actively taking cannabinoids were younger than patients with no history of cannabinoid use (41.0 ± 15.4 vs 48.0 ± 15.9 years; $P < 0.01$). Most patients in our study were females (80.7%) and whites (80.2%), with a mean BMI of 27.1 ± 7.7. There were no differences between cannabinoid users and nonusers with respect to their gender, race, or BMI. A fourth of the patients (25.3%) in our study reported active alcohol use, with a minority (15.7%) actively smoking tobacco. The patients with active cannabinoid use were more likely to report concomitant tobacco use compared with cannabinoid-naive patients (25.7% vs 9.5%; $P < 0.01$), with no difference in the prevalence of alcohol use (30% vs 24.8%;

Table 4. Demographics, social history, duration of symptoms, GES results, medication use, and surgical treatments of Gp and in patients with Gp and related disorders, including patients actively on cannabinoids and patients with no history of cannabinoid use

Factor	All patients (N = 197)	Patients currently on cannabinoids (n = 70)	Patients with no history of cannabinoid use (n = 105)	*P* value
Age (yr)	44.9 ± 15.9	41.0 ± 15.4	48.0 ± 15.9	**<0.01**
Gender (% female individuals)	159 (80.7%)	57 (81.4%)	85 (81.0%)	0.94
Race (% whites)	158 (80.2%)	55 (78.6%)	83 (79.0%)	0.94
BMI (kg/m^2)	27.1 ± 7.7	26.7 ± 8.1	27.9 ± 7.7	0.33
Current tobacco use	31 (15.7%)	18 (25.7%)	10 (9.5%)	**<0.01**
Current alcohol use	50 (25.3%)	21 (30.0%)	26 (24.8%)	0.44
Duration of symptoms (yr)	7.6 ± 7.0	8.5 ± 7.3	7.4 ± 7.0	0.35
Hot showers for the relief of symptoms	67 (34.0%)	26 (37.1%)	27 (25.7%)	0.11
Anti-emetic use	171 (86.8%)	60 (85.7%)	90 (85.7%)	1.00
Current use of other alternative or complementary treatments[a]	91 (46.2%)	34 (48.6%)	47 (44.8%)	0.62
Opioid use	61 (31.0%)	21 (30.0%)	32 (30.5%)	0.95
History of gastric stimulator	62 (31.5%)	17 (24.3%)	35 (33.3%)	0.20
History of pyloromyotomy	11 (5.6%)	4 (5.7%)	5 (4.8%)	0.78
History of feeding tubes[b]	25 (12.7%)	8 (10.8%)	10 (9.5%)	0.78
Delayed gastric emptying	154 (78.2%)	52 (74.3%)	87 (82.9%)	0.17
Type of Gp				0.84
Idiopathic	64 (41.6%)	20 (38.5%)	35 (40.2%)	
Diabetic	57 (37.0%)	22 (42.3%)	33 (37.9%)	
Atypical[a]	28 (18.2%)	9 (17.3%)	15 (4.6%)	
Postsurgical[b]	5 (3.2%)	1 (1.9%)	4 (17.2%)	
GES: retention at 2 h (%)	58.5% ± 20.8%	57.2% ± 22.4%	59.2% ± 20.7%	0.60
GES: retention at 4 h (%)	27.5% ± 21.3%	29.2% ± 23.9%	27.2% ± 20.3%	0.60

Results are expressed as mean ± s.d. or percentages. *P* value (calculated using Student *t* test or χ^2 test as appropriate) compares patients actively using cannabinoids with patients with no history of cannabinoid use.
BMI, body mass index; GES, gastric emptying scintigraphy; Gp, gastroparesis.
[a]Patients *actively* taking alternatives or complementary treatments included probiotics (n = 58), ginger (n = 40), herbal supplements (n = 12), acupuncture (n = 9), massage therapy (n = 3), acupressure (n = 2), chiropractor treatments (n = 2), hypnosis (n = 2), apple cider vinegar (n = 1), holy basil (n = 1), melatonin (n = 1), peppermint oil (n = 1), and turmeric (n = 1).
[b]Including patients with a history of G-tubes, J-tubes, or GJ-tubes.
Valued in bold are statistically significant.

P = 0.44). There was a trend for cannabinoid-using patients to be more likely to take hot showers for the relief of their symptoms compared with cannabinoid nonusers (37.1% vs 25.7%; *P* = 0.11).

Other alternative and complementary treatments

More than half of the patients (n = 114, 57.9%) in our study reported current (n = 91) or past (n = 23) use of other alternative or complementary treatments (Table 2). The most commonly used other complementary treatments were probiotics (n = 81). Nearly half of the patients (44.4%) with active or past probiotics use reported improvement in their GI symptoms. The patients actively using probiotics (n = 58) had a higher severity of symptoms on bloating subscale (3.5 ± 1.4 vs 2.8 ± 1.6; *P* = 0.01), with no differences in the GCSI total score, nausea/vomiting subscore, postprandial fullness/early satiety subscore, or abdominal pain subscores compared with patients with no active or history of probiotics use (n = 116). Other commonly used alternative treatments (active or past use) included ginger (n = 56), acupuncture (n = 30), and herbal supplements (n = 23). Many patients using these other alternative treatments also had improvements in their symptoms, including ginger (57.1%), acupuncture (33.3%), and herbal supplements (39.1%). There was no difference between cannabinoid users and nonusers in their likelihood of using other alternative/complementary treatments.

DISCUSSION

In this study of patients with Gp and related disorders (functional dyspepsia and CNVS), we found that over a third of these patients (35.5%) report active use of cannabinoids, most commonly marijuana (24.9%). Most of these patients use cannabinoids for the relief of their chronic symptoms of Gp and related disorders, typically nausea, vomiting, abdominal pain, and/or loss of appetite. Most patients with symptoms of Gp and related disorders

perceive improvement in their symptoms with cannabinoids. These patients using cannabinoids are younger and more symptomatic with a higher severity of GI symptoms compared with cannabinoid nonusers.

The rate of active marijuana use in our study (24.9%) was higher than 14.6% in the general adult US population (5). However, only a minority of the cannabinoid-using patients in our study reported using medical marijuana. Possible reasons could include the relatively short period of time marijuana has been available for medical prescription in Pennsylvania, limited healthcare providers who are licensed to prescribe it, lack of patient awareness of its availability, and/or lack of coverage by the health insurance companies. Our findings of higher rates of cannabinoid use in younger patients are similar to the patients with IBD (18). Male individuals and African Americans have been reported to have the highest rate of cannabinoid use (19, 20); however, in our study we did not find any gender or racial differences between cannabinoid-using and cannabinoid-naive patients. Historically, the most common way of using *Cannabis* has been through smoking (21), which was also seen in our study.

Cannabinoids may have therapeutic potential in patients with GI disorders. Among patients with Crohn's disease, most of the patients (83.9%) who use *Cannabis* report improvement in their abdominal pain with *Cannabis* (7). However, *Cannabis* use has also been associated with worse disease prognosis in patients with Crohn's disease and with the need for surgical interventions in these patients (7). In our study, most patients taking cannabinoids for the symptoms of Gp and related disorders reported improvement in their symptoms with cannabinoids. The perceived benefit was seen in patients taking natural (THC and/or CBD) and synthetic cannabinoids (dronabinol), although patients taking natural cannabinoids more commonly reported improvement in their symptoms of Gp and related disorders. Cannabinoid-using patients were equally likely to have a history of surgical interventions for their symptoms of Gp (including gastric stimulators, pyloromyotomy, and/or feeding tubes), when compared with cannabinoid-naive patients. Although relatively small sample size (n = 24) and lack of control group, a recent preliminary report of a study prescribing natural and/or synthetic cannabinoids in patients with refractory Gp also showed significant improvement in several symptoms of Gp with cannabinoids in these patients (22). Cannabinoids have been shown to have analgesic effects on both spinal and peripheral levels in the GI tract and mediate their anti-emetic effects via CB1 receptors in the dorsal vagal complex of the brainstem (23). Interestingly, we found no difference between cannabinoid users and cannabinoid-naive patients in their use of anti-emetics. This could be due to significantly higher underlying disease severity in cannabinoid-using patients, particularly the symptoms of nausea and vomiting. Our study did not explore the extra GI negative effects of cannabinoids. Previous studies have suggested that *Cannabis* use may be associated with several acute adverse effects (including anxiety, paranoia, memory lapses, impaired motor coordination, and reaction time increasing the risk of accidents) and long-term effects (such as cognitive impairment, decreased life satisfaction, increased risk of psychotic disorders, and potential for abuse and addiction) (24–26). The efficacy and safety of cannabinoids in patients with symptoms of Gp and related disorders should be further studied.

Patients with symptoms of Gp and related disorders who were using cannabinoids had an increased symptom burden of Gp as evidenced by a higher severity of several important symptoms of Gp compared with cannabinoid nonusers, including nausea, vomiting, abdominal pain, and loss of appetite. Studies on patients with IBD have also shown cannabinoids users to have a higher disease severity compared with cannabinoid nonusers (27). Paradoxically, cannabinoids are known to delay gut motility (3). Dronabinol has been shown to delay gastric emptying and increase fasting gastric volumes, without any changes in gastric accommodation (28). With the legalization of natural cannabinoid use for medicinal purposes, studies with quantitative data on the effects of natural cannabinoids on gastric emptying and fundic accommodation in patients with GI motility and functional disorders will be useful. In our study, we did not find any differences in gastric emptying between cannabinoid-using and cannabinoid-naive patients with symptoms of Gp and related disorders; however, we do not have the gastric emptying of the patients before and after they started using cannabinoids. Previous studies have shown a poor correlation between symptom severity and gastric retention in patients with Gp (29,30).

Nearly a third of patients (31%) in our study reported opioid use. Chronic use of opioids in patients with Gp has been associated with higher severity of Gp symptoms and increased healthcare use (31). In the era of the opioid epidemic, it has been proposed that cannabinoids may play an important role in the management of opioid use disorder (32). However, a recent study in patients with chronic noncancer pain suggested that cannabinoids may not have an opioid-sparing effect (33). In our study, we did not see any difference in the prevalence of opioid use between cannabinoid-using and cannabinoid-naive patients with symptoms of Gp and related disorders. A preliminary report suggested that cannabinoids reduce abdominal pain in patients with Gp (34).

Our study shows that cannabinoid-using patients with symptoms of Gp and related disorders more commonly report concomitant tobacco use (25.7% vs 9.5%; $P < 0.01$). A recent study using data from the National Survey on Drug Use and Health also concluded that despite the decrease in cigarette smoking in the United States, cigarette smoking is on the rise in active *Cannabis* users (35). We saw a trend for cannabinoid users with symptoms of Gp and related disorders to more frequently take hot showers for the relief of their Gp symptoms compared with cannabinoid nonusers. Hot showers for the relief of GI symptoms have been associated with CHS (36). Our patients did not have CVS or CHS as questioned by the Rome IV Diagnostic Questionnaire.

Patients with symptoms of Gp and related disorders frequently use other alternative and complementary treatments as well for their chronic GI symptoms. Most commonly used alternative and complementary treatments seen in our patient population were probiotics, ginger, and acupuncture, with many patients reporting improvement in their Gp symptoms with these treatments. Probiotics are known to improve symptoms in GI disorders characterized by dysbiosis, such as irritable bowel syndrome, by targeting intestinal microbiota (37,38). In our study, the patients who were using probiotics for their symptoms of Gp and related disorders had a higher severity of bloating compared with nonusers, which corroborates the findings of Hasler et al. (39). From our study, we cannot tell whether the patients were using probiotics to help with their symptom of bloating, or the higher severity of bloating in these patients was an adverse effect of probiotics use. Gp is commonly associated with intestinal bacterial overgrowth—an important cause of bloating, and it is possible that the therapeutic benefit of probiotics in patients with Gp may in part be secondary to their effects on

intestinal microbiota (40,41). Probiotics may improve GI symptoms in patients with other functional bowel disorders as well (42). Studies suggest that probiotics, ginger, and acupuncture cause some of their therapeutic effects by modulating the endocannabinoid pathway (43–45). Further studies exploring the therapeutic potential and safety profile of these alternative and complementary treatments in patients with symptoms of Gp will be useful.

Our study has some limitations. As an epidemiologic study, our sample size was limited. In the future, additional studies using a larger sample size to validate our findings will be useful. We recruited consecutive patients seen on follow-up at our Motility Center to decrease sampling bias. Nonetheless, as cannabinoids are known to have anti-emetic effects and analgesic effects, it is plausible that cannabinoid -users may be more inclined to participate in a study on the perceived benefit of cannabinoids on GI symptoms. We do not have the symptom severity of the patients before they started using cannabinoids to quantify the improvement in symptoms and only reported the patients' perceived benefit of cannabinoids and other alternative/complementary treatments. As patients were not blinded on the specific aims of the study, this may have been a source of reporting bias. However, this would be applicable to patients taking all alternative and complementary treatments, yet the perceived benefit of natural cannabinoids was more pronounced than other complementary/alternative treatments. The patients in our study were generally referred from community settings, and it is conceivable that the patients referred to our tertiary care center may represent a more severe spectrum of the disease. This might also reflect that 31.5% of our patients had a history of gastric stimulators. Our study was a questionnaire-based study. Some of the questions on the perceived benefit of alternative/complementary were not answered by all patients; however, all patients taking natural cannabinoids reported the perceived benefit of these cannabinoids. Last, because this is a questionnaire-based study, there is a potential of recall bias as well. This would likely apply to both cannabinoid-using and cannabinoid-naive patients with Gp symptoms.

In conclusion, a third of patients with Gp and related disorders actively use cannabinoids to address their symptoms. These patients using cannabinoids are younger and more symptomatic compared with cannabinoid-naive patients. Most of these patients report improvement in their symptoms of Gp with cannabinoids. With the legalization of *Cannabis* use in some states and the setting of medical marijuana distribution centers, the use of marijuana in patients with Gp may increase. Given the concerns of possible adverse effects of cannabinoids, placebo-controlled, randomized, double-blind studies on the efficacy and safety of cannabinoid use will be useful to understand the benefit of cannabinoids and minimize the risks associated with their use in patients with GI motility and functional disorders.

CONFLICTS OF INTEREST

Specific author contributions: A.J. helped in the study planning, collected and analyzed the data, did literature review, and wrote the manuscript. H.P.P. planned the study, evaluated patients included in the study, did literature review, and helped write the manuscript. Both authors approved the final version of the manuscript.
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Study Highlights

WHAT IS KNOWN

- ✓ Natural and synthetic cannabinoids are being increasingly used for medicinal and recreational purposes in the United States.
- ✓ A considerable number of patients with GI disorders use cannabinoids with perceived benefit.
- ✓ We do not know the prevalence and benefit of cannabinoid use in patients with symptoms of Gp and the characteristics of these cannabinoid-using patients.

WHAT IS NEW HERE

- ✓ A third of patients with symptoms of Gp actively use cannabinoids, most commonly smoking marijuana.
- ✓ Patients with symptoms of Gp taking cannabinoids are younger and more symptomatic than those not taking cannabinoids.
- ✓ Most patients with symptoms of Gp perceive improvement in their symptoms with cannabinoids.

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