EVIDENCE-BASED GI
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Cannabidiol: A Potential Therapeutic Option for Idiopathic and Diabetic Gastroparesis

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This summary reviews Zheng T, BouSaba J, Taylor A, et al. A randomized controlled trial of efficacy and safety of cannabidiol in idiopathic and diabetic gastroparesis. Clin Gastroenterol Hepatol 2023 Jul 22;S1542-3565(23)00543-8. Epub ahead of print. doi: 10.1016/j.cgh.2023.07.008.

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STRUCTURED ABSTRACT

Question: Does 4 weeks of treatment with cannabidiol (CBD) provide symptom relief compared to placebo in patients with idiopathic or diabetic gastroparesis?

Design: Randomized, double-blinded, placebo-controlled (1:1), parallel-design, 4-week study, between September 2020 and March 2023.

Setting: Mayo Clinic, Rochester, Minnesota.

Participants: Symptomatic individuals with scintigraphic evidence of delayed gastric emptying (≤ 25% emptied at 2 hours and/or ≥75% emptied at 4 hours) for at least 3 months were eligible for participation. Patients with post-surgical gastroparesis were excluded from the study.

Intervention/Exposure: Twice daily, oral Cannabidiol, in divided doses starting at 2.5 mg/kg/day, and increased by 2.5-5.0 mg/kg/day until the target dose of 20 mg/kg/day.

Outcomes: The primary end point was change in patient response based on the Gastroparesis Cardinal Symptom Index Daily Diary (GCSI-DD) score, which was appraised daily and summarized for the 4-week treatment period. Secondary end points included aggregate symptoms during the 4 hours after the standard meal for the gastric emptying study (GES), and pharmacodynamics such as GES lag time, percentage of solid meal emptied at 1, 2, 4 hours, and maximum tolerated volume (MTV). Aggregate symptoms scored 30 minutes after MTV was also estimated. Other secondary end points included individual symptoms on the GCSI-DD. An exploratory end point was the association of fatty acid amide hydrolase (FAAH) and cannabinoid receptor 1 (CNR1) with responses to treatment.

Data Analysis: Statistical analysis compared changes in patient responses and pharmacodynamic outcomes (from baseline to while on treatment) between both intervention and placebo arms of the trial using analysis of variance. A sample size of 44 was determined after an interim analysis of 24 participants. Baseline measurements and body mass indices were used as covariates.

Funding: National Institute of Health RO1 grant (R01-DK122280).

Results: Among 44 study patients, mean age was 44.0 years; 89% female; 89% White; and 73% with idiopathic gastroparesis. Ninety-five percent of participants completed 4 weeks of treatment. Both groups were matched for age, sex, race, body mass index, and baseline gastric emptying. Compared to the placebo group, patients in the CBD group had slower gastric emptying parameters, but also had significantly lower GCSI scores (P=0.008), lower scores for inability to finish a meal (P=0.029), fewer episodes of vomiting in a 24-hour period (P=0.006), and lower perceived severity of gastroparesis symptoms (P=0.034). Importantly, no significant differences in lab values between both groups was observed. Also, no difference was seen in nausea and fatigue, though patients in the CBD group reported more diarrhea. Relevant pharmacodynamic outcomes are highlighted in **Table 1**.

COMMENTARY

Why Is This Important?

Gastroparesis significantly impacts patient quality of life and is associated with substantial health resource utilization including hospitalizations[1]. In addition, the number of inpatient admissions and associated costs in the United States is on the increase[1]. This is likely related to the limited therapeutic options available for managing gastroparesis, especially in the United States. Presently, metoclopramide is the only medication approved for the management of gastroparesis by the Food and

	Cannabidiol (n=21)	Placebo (n=23)	*P* value
Fasting gastric volume (ml)	276.2 (222.8-329.6)	257.8 (206.8-308.8)	0.616
Accommodation gastric volume (ml)	435.5 (396.8–474.1)	405.0 (368.1–441.9)	0.255
Fullness kcal on nutrient drink test	817.1 (719.9–914.3)	665.4 (572.5–758.2)	0.028
Maximum kcal on nutrient drink test	1114.7 (981.8–1247.7)	889.3 (762.2–1016.3)	0.018
Gastric emptying at 4 hours, %	52.2 (44.8–59.6)	62.8 (55.8–69.9)	0.045

Table 1. Effect of cannabidiol and placebo on pharmacodynamic end points in gastroparesis.

Drug Administration (FDA) and prescription comes with a black box warning because it crosses the blood-brain barrier and is associated with extrapyramidal side effects including tardive dyskinesia[2]. Motilin receptor agonists (e.g. erythromycin) and the 5-HT4 receptor agonist, prucalopride, are often used off-label with varying levels of success[2]. As such, novel therapeutics are needed to manage this chronic condition. Zheng et al, in this randomized clinical trial, attempt to address this unmet need by investigating the efficacy and safety of pharmaceutical grade CBD on gastroparesis symptoms.

Cannabidiol or CBD is the second most prevalent active ingredient in marijuana after THC or tetrahydrocannabinol, which is the primary psychoactive agent in marijuana. CBD is a cannabinoid receptor 2 inverse agonist with central nervous system mediated effects. That helps explain why CBD, which is widely available as oils, gummies, and capsules, has been purported to improve anxiety, insomnia, and chronic pain. It's also reported to impact visceral or somatic sensation peripherally and is anti-inflammatory, which makes it an attractive alternative therapy for patients with gastroparesis.

Key Study Findings

In this single center study of 44 participants, the authors show that

CBD lowered GCSI-DD scores, reduced severity of symptoms, including the inability to finish a normal meal, and reduced number of vomiting episodes despite slowing of solid food gastric emptying.

Caution

This is a small, single-center study

which limits generalizability. Though adequately powered to detect differences in outcomes, most participants in the study (73%) had idiopathic gastroparesis. Patients with post-surgical gastroparesis were excluded. Since the study duration was 4 weeks, the sustainability of the benefit from CBD and its impact on reducing gastroparesis flares and subsequent hospitalizations could not be ascertained. Nevertheless, given the lack of effective therapies for gastroparesis, this is an important first step in identifying new therapeutics for this disabling disorder.

My Practice

Medical grade cannabidiol as used in this study is currently FDA approved for seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome, or tuberous sclerosis complex (TSC); therefore, I [L.B.N.] have no experience with this compound. However, cannabis and cannabinoids are being used by gastroparesis patients. The NIH Gastroparesis Consortium reported 12% of patients used marijuana and those with more severe nausea or abdominal pain were more likely to use marijuana[3]. In our [Stanford] survey of patients with chronic nausea, 15% of patients reported marijuana was the most effective treatment for their symptoms[4]. Based on this data, it is important to be able to counsel patients about cannabis use and know the laws in the state where you practice. In California, physicians can recommend but not prescribe cannabis. For patients who have symptoms of nausea or pain refractory to anti-emetics and neuromodulators who are interested in trying CBD, I recommend working with a dispensary that can formulate a product that has more CBD than tetrahydrocannabinol (THC). As with most therapies, I recommend starting low and titrating slowly to the lowest effective dose. I do not prescribe dronabinol (Marinol) which is a synthetic THC due to central nervous system effects and the effects of THC on gastric motility by slowing gastric emptying. I do not recommend CBD as first line therapy; however, it should be an option considered in patients with medically refractory symptoms while FDA approved therapies for gastroparesis remain elusive.

For Future Research

Multi-center clinical trials with larger and more diverse patient populations and longer study duration are warranted to see if these benefits from CBD can be replicated. This would also allow exploration of any subgroup differences in efficacy based on the etiology of gastroparesis. Studies that evaluate the efficacy of CBD in combination with other therapeutic agents, such as metoclopramide, on patient reported outcomes and healthcare resource utilization would also be helpful.

Conflicts of Interest

Drs. Okafor and Nguyen report no potential conflicts of interest related to this article.

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