DEPARTMENT OF HEALTH

Gastroparesis Issue Brief

OCTOBER 2022

Introduction

This briefing was prepared in response to a petition to consider adding gastroparesis as a new condition to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, members of the Medical Cannabis Review Panel, and interested members of the public, scientific studies of cannabis products as a therapy for the petitioned condition. Brief information on the condition and its current treatment are provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) were included, especially if there are few clinical trials or observational studies. Interpretation of surveys can be difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses; however, surveys published in peer-reviewed journals were included for completeness. Published recommendations or opinions of national medical organizations were also included.

Searches for published clinical trials and observational studies of cannabis therapy were conducted using the National Library of Medicine's Medline key word searches appropriate for the petitioned condition. Articles identified as clinical trials, observational studies, or review articles were collected and reviewed. References in the identified articles were examined to ensure all the articles associated with the petitioned condition were identified and included. Moreover, clinicaltrials.gov, a federal government-maintained website responsible for tracking current clinical trials funded, was used to identify any ongoing or completed clinical trials.

Definition

Gastroparesis, also known as delayed gastric emptying, is a disorder that slows or stops the movement of food from a patient's stomach to a patient's small intestine (Camilleri et al., 2018). Typically, after a patient eats food, the muscles in the wall of the stomach grind the food into small pieces and pushes them into the small intestine to continue being digested. However, the stomach muscles of patients with gastroparesis work poorly or not at all, resulting in an inability to empty the food from their stomach normally (Camilleri et al., 2018).

Symptoms of gastroparesis include:

- Feeling full soon after starting a meal
- Feeling full long after eating a meal
- Nausea
- Vomiting
- Excessive bloating

- Excessive belching
- Pain in the upper abdomen
- Heartburn
- Poor appetite

Epidemiology

A study by Ye et al. 2021 estimated an overall standardized prevalence of gastroparesis at 267.7 per 100,000 (Ye et al., 2021). Further, subgroup analysis found that the prevalence of gastroparesis was greater than twice as common in females than in males (Ye et al., 2021). Gastroparesis is more common in patients aged 58 to 64 years, and lowest in patients aged 18 to 27 years (Ye et al., 2021).

The prevalence of diabetic gastroparesis was found to be 101.4 per 100,000 persons (Ye et al., 2021). Moreover, the prevalence of diabetic gastroparesis among type 1 and type 2 diabetics was 10.4 per 100,000 persons and 91.0 per 100,000 persons, respectively (Ye et al., 2021). Whereas the prevalence of idiopathic gastroparesis was 24.8 per 100,000 persons. Subgroup analysis of diabetic gastroparesis noted that the prevalence was higher in females than in males and greater in patients aged 58 to 64 years compared to patents aged 18 to 27 years (Ye et al., 2021). Further, elevated blood glucose concentrations (>8 mmol/L) are associated with delayed gastric emptying (Camilleri et al., 2018).

In addition to diabetes, other known gastroparesis causes include:

- Injury to the vagus nerve due to surgery on the esophagus, stomach, or small intestine
- Hypothyroidism
- Certain autoimmune diseases (e.g., scleroderma)
- Certain nervous system disorders (e.g., Parkinson's disease)
- Viral stomach infections
- Bacterial overgrowth in the small intestinal

Diagnosis of Gastroparesis

Health care professionals use medical history, a physical exam of symptoms, and several tests to diagnose gastroparesis and rule out conditions that may cause similar symptoms (National Institute of Diabetes and Digestive and Kidney Diseases, NIDDK).

The most important test used in making a diagnosis of gastroparesis is a Scintigraphy. This test involves eating a light meal, such as eggs and toast, which contains a small number of radioactive materials. A scanner is then used to detect the movement of the above-mentioned radioactive material within the food as it leaves a patient's stomach (NIDDK).

Additionally, a breath test is used to measure how fast the stomach empties after consuming food. During this test, a patient consumes solid or liquid food that contains a substance that their body absorbs. After some time, the substance can be detected in the patient's breath. Measurements are made every few hours. This test shows how fast the stomach empties after consuming food by measuring the amount of substance released over a constant period (NIDDK).

A health care provider can also use an upper gastrointestinal (GI) endoscopy to visually examine the upper digestive system, including the esophagus, stomach, and beginning of the small intestine (duodenum) of patients. Finally, a health care provider can use an ultrasound to develop a high-frequency sound wave image of the stomach (NIDDK).

Current Therapies

Treating gastroparesis begins with identifying and treating the underlying condition. Therefore, if a patient has diabetes, a health care provider will work with the patient to help control their diabetes to control their gastroparesis. Currently, health care workers recommend avoiding large, high-caloric, fatty meals, as well as dietary fibers and foods that have been identified by the individual patient as an agitator of the symptoms (Grover et al., 2019). Notably, these medical recommendations have never been validated in appropriate validation studies (Grover et al. 2019). A randomized controlled trial of patients with diabetic gastroparesis noted that small particle-sized solids was associated with improved reflux symptoms, the feeling of fullness, nausea, vomiting, and bloating (Grover et al. 2019). However, another study noted that only one-third of patients with gastroparesis received nutritional counseling and only 2% were following any dietary suggestions. This suggests that lifestyle changes alone are inadequate from a practical standpoint for managing gastroparesis in the majority of patients.

Ideally, therapy for gastroparesis should include a combination of reversing cellular defects, accelerating gastric emptying, and improving cardinal symptoms. However, gastric emptying is only partially related to clinical manifestation of gastroparesis and other mechanisms are potentially involved following initial disease onset, including decreased gastric accommodation, small bowel motor abnormalities, and visceral hypersensitivity (Grover et al., 2019).

Medications

A recent meta-analysis confirmed the efficacy of prokinetics as a therapy for gastroparesis clinical symptoms, but most studies are old with poor study quality that do not match current requirements of health authorities in North America and Europe (Pittayanon et al., 2019). Prokinetics is a class of medication designed to promote movement of food in the gut (motility). Metoclopramide is the only prokinetics available in the U.S. (Grover et al., 2019). However, its use is restricted by the FDA to 12 weeks. The restriction is because metoclopramide can cross the blood-brain barrier and can cause feelings of anxiety, depression, tremors, involuntary movements, and other severe side effects

In addition to prokinetics, a patient might be prescribed an antiemetic, a class of medication used to treat nausea and vomiting. Importantly, this class of drugs has been identified as effective at treating nausea and vomiting in cancer patients. However, only two trials have assessed the efficacy of these antiemetics. Only one study was able to confirm the efficacy of antiemetics drugs on gastroparesis in a predominantly female population. This medication has no impact on gastrointestinal motility (Pittayanon et al., 2019).

Treatment – Endoscopic and Surgical

Using high frequency electrical pulses delivered to the smooth muscle of the lower stomach, a method known as gastric electrical stimulation, aims to modulate the afferent pathway and reduce gastroparesis symptoms. However, a prospective cohort study exploring the efficacy of gastric electrical stimulation, by the National Institutes of Health, found that it only reduced nausea symptoms (Zheng et al., 2021). Several studies have found the gastric electrical stimulation can reduce vomiting frequency, improve GI symptoms, increase glycemic control, and improve quality of life indicators (Pittayanon et al., 2019). However, only three of these studies were controlled trials, and only one of these showed partially positive results. As a result, the evidence from controlled trials does not support the use of gastric electrical stimulation (Zheng et al., 2021).

Alternatively, researchers have suggested using botulinum toxin as a way to relax the lower esophagus so that food and liquid can move more easily through the digestive tract (Pittayanon et al., 2019). However, only two randomized controlled trials have assessed the efficacy. Both studies failed to obtain enough samples to see a significant association and found no difference in symptom improvement between the treatment and placebo. As a result, there is no clinical evidence supporting the widespread use of Botox injections in the treatment of gastroparesis (Pittayanon et al., 2019).

Neuromodulators, such as Levosulpiride, have been identified as a potential therapy for accelerating gastric emptying (Pittayanon et al., 2019). It has been shown to improve symptoms in patients with both diabetic gastroparesis and idiopathic gastroparesis. But this did not correlate with the acceleration of gastric emptying (Grover et al., 2019). As a result, the efficacy of this medication in the treatment of gastric emptying remains to be confirmed.

Pyloromyotomy (a surgical treatment) has resurged as a possible potential treatment for gastroparesis. One study noted that 70% of gastroparesis patients experienced loss of muscle tissue surrounding the entrance to the small intestine (Pittayanon et al., 2019). Multiple studies have shown improvements in nausea and vomiting. Improvements in pain were reported in a few studies, with pain reduction declining after 6 months. However, the effectiveness of the treatment varies by methods used. Few clinical trials have assessed the best treatment methodologies (Pittayanon et al., 2019). As a result, more clinical trials are needed to determine the most effective pyloromyotomy method, and the long-term effect of surgery remains to be seen.

Overall, treatments such as Tricyclic antidepressants have been identified as ineffective in the treatment of gastroparesis (Pittayanon et al., 2019). Antiemetic NK1 receptor antagonists appear to have some effectiveness. However, more research is needed. Further, prokinetic serotonergic treatments such as Prucalopride require more research (Pittayanon et al., 2019). Both Fundic relaxants and Pyloric therapies require more research in order to determine the efficacy of both medications as a treatment for gastroparesis (Pittayanon et al., 2019). Finally, there is no controlled evidence for immune-based therapies in gastroparesis (Pittayanon et al., 2019).

Certain medicines may delay gastric emptying or affect motility, resulting in symptoms that are like those of gastroparesis. Medicines that may delay gastric emptying or make symptoms worse include the following:

- Narcotic pain medicines, such as codeine, hydrocodone, morphine, oxycodone, and tapentadol
- Some antidepressants, such as amitriptyline, nortriptyline, and venlafaxine
- Some anticholinergics — medicines that block certain nerve signals
- Some medicines used to treat overactive bladder
- Pramlintide

Pre-clinical Research

Research has shown that gastric emptying is physiologically regulated by the endocannabinoid system (Marzo et al., 2009). More specifically, some animal studies suggest that compounds that inhibit endocannabinoid activity encourages gastric emptying, which, if the results translate to human populations, would be the desired effect for gastroparesis patients. Pre-clinical studies have found an association between gastrointestinal dysmotility (abnormal intestinal contractions) and altered expression of the cannabinoid one (CB1) and cannabinoid two (CB2) receptors (Daniel et al., 2020). Activation of CB1 receptors suppresses motility and can be increased when there is inhibition of degradative enzymes or reversed by inhibition of endocannabinoid synthesis (Daniel et al., 2020). Further, fatty acid amide hydrolase (FAAH), an enzyme associated with the endocannabinoid system, has been associated with an ability to modify stool to an acceptable consistency and move the stool from the cecum to the rectosigmoid area (Maselli et al., 2020). Studies have shown that the cannabinoid, such as dronabinol and delta 9-THC, delays gastric emptying of solids (exacerbates gastroparesis), and cannabinoids inhibit colonic contractility, decreasing intragastric pressure (exacerbates gastroparesis) (Hornby et al., 2004). Whereas, the use of inhibitors that inhibit synthesis of endocannabinoids, accelerated colonic transit (remedying gastroparesis) in mice (Maselli et al., 2020).

Clinical Trials

A double-blind randomized control trial by McCallum et al. (2019) showed that the administration of delta-9-THC one hour prior to a meal resulted in delayed gastric emptying, exacerbating gastroparesis, of radiolabeled solid food in nine males and four females, which mirrors the preclinical research summarized above. However, a study by Bateman et al. (1983) reported no difference in gastric emptying of seven cannabis-naive male volunteers compared to placebo controls (Bateman et al., 1983). Both studies are limited in their interpretive power, however, given their small sample sizes. In addition, Bateman et al. (1983) only reported on male participants, which puts limits on generalizability of findings across genders.

A more recent clinical trial by Esfandyari et al. (2006), found that dronabinol was associated with a significant delay in gastric emptying (which should be avoided) of standard solid and liquid meals. However, there seemed to be a difference in females compared to males, with females having a significantly slower gastric emptying. Overall, the current clinical trial literature suggests an association between the use of cannabis and delayed gastric emptying (which should be avoided). However, these studies were limited by low sample sizes, and limited generalizability.

Observational Studies

Pre-clinical work suggest that medical cannabis may delay gastric emptying (which should be avoided) while observational studies remain limited and inconclusive (Daniel et al., 2020). A limited number of observational studies have been published evaluating the association between cannabis use and gastroparesis. Notably, multiple observational studies assessing the association between cannabis use and gastroparesis symptoms found that patients who reported using cannabis also reported experiencing less severe symptoms compared to non-users. A study by McCarty et al. (2022) noted that patients with gastroparesis and cannabis use were younger, had a lower social economic status, and were disproportionately affected by psychiatry diagnoses. However, they had better hospitalization outcomes, including decreased length of stay and improved in-hospital mortality. Further, studies by Parkman et al., published in 2019 and 2020, reported that patients using cannabis perceived an improvement in their symptoms following use of cannabinoids.

In a 2022 study by Muacevic et al. (2022), the association between different cannabinoids and gastroparesis was conducted. The study noted that marijuana was more effective than dronabinol at reducing symptom severity, and both cannabinoids (marijuana and dronabinol) showed promise as a novel therapy for gastroparesis. Data from Barbash et al. (2019) noted a decrease in all gastroparesis symptoms following the use of a cannabinoid, with marijuana having the highest effect on reducing symptoms. In contrast, work by Jehangir et al. (2019) found no association between cannabis use and gastroparesis (Jehangir et al., 2019). Overall, observational studies have shown a clear association between cannabinoid use and reduced gastroparesis symptoms. However, these studies are limited by the fact that they are observational studies and thus can only show associations and not causation.

National Medical Organization Recommendations

The American College of Gastroenterology states that marijuana (THC) significantly delays gastric emptying and should be avoided by patients with gastroparesis.

References

Bateman D. N. (1983). Delta-9-tetrahydrocannabinol and gastric emptying. *British journal of clinical pharmacology*, *15*(6), 749–751. https://doi.org/10.1111/j.1365-2125.1983.tb01561.x

Barbash, B., Mehta, D., Siddiqui, M. T., Chawla, L., & Dworkin, B. (2019). Impact of Cannabinoids on Symptoms of Refractory Gastroparesis: A Single-center Experience. *Cureus*, *11*(12), e6430. https://doi.org/10.7759/cureus.6430

Camillri, M., Chedid, V., Ford, A. C., Haruma, K., Horowitz, M., Jones, K. L., Low, P. A., Park, S. Y., Parkman, H. P., & Stanghellini, V. (2018). Gastroparesis. *Nature reviews. Disease primers*, *4*(1), 41. https://doi.org/10.1038/s41572-018-0038-z

Di Marzo, V., Capasso, R., Matias, I., Aviello, G., Petrosino, S., Borrelli, F., Romano, B., Orlando, P., Capasso, F., & Izzo, A. A. (2008). The role of endocannabinoids in the regulation of gastric emptying: alterations in mice fed a high-fat diet. *British journal of pharmacology*, *153*(6), 1272–1280. https://doi.org/10.1038/sj.bjp.0707682

Esfandyari, T., Camilleri, M., Ferber, I., Burton, D., Baxter, K., & Zinsmeister, A. R. (2006). Effect of a cannabinoid agonist on gastrointestinal transit and postprandial satiation in healthy human subjects: a randomized, placebo-controlled study. *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society*, *18*(9), 831–838. https://doi.org/10.1111/j.1365-2982.2006.00834.x

Grover, M., Farrugia, G., & Stanghellini, V. (2019). Gastroparesis: a turning point in understanding and treatment. *Gut*, *68*(12), 2238–2250. https://doi.org/10.1136/gutjnl-2019-318712

Hornby, P. J., & Prouty, S. M. (2004). Involvement of cannabinoid receptors in gut motility and visceral perception. *British journal of pharmacology*, *141*(8), 1335–1345. https://doi.org/10.1038/sj.bjp.0705783

Jehangir, A., & Parkman, H. P. (2019). Cannabinoid Use in Patients with Gastroparesis and Related Disorders: Prevalence and Benefit. *The American journal of gastroenterology*, *114*(6), 945–953. https://doi.org/10.14309/ajg.0000000000000181

Jung, H. K., Choung, R. S., Locke, G. R., 3rd, Schleck, C. D., Zinsmeister, A. R., Szarka, L. A., Mullan, B., & Talley, N. J. (2009). The incidence, prevalence, and outcomes of patients with gastroparesis in Olmsted County, Minnesota, from 1996 to 2006. *Gastroenterology*, *136*(4), 1225–1233. https://doi.org/10.1053/j.gastro.2008.12.047

Maselli, D. B., & Camilleri, M. (2021). Pharmacology, Clinical Effects, and Therapeutic Potential of Cannabinoids for Gastrointestinal and Liver Diseases. *Clinical gastroenterology and hepatology: the official clinical practice journal of the American*

Gastroenterological Association, *19*(9), 1748–1758.e2. https://doi.org/10.1016/j.cgh.2020.04.020

McCallum, R. W., & Bashashati, M. (2019). Cannabis for Gastroparesis: Hype or Hope?. *The American journal of gastroenterology*, *114*(6), 865–866. https://doi.org/10.14309/ajg.0000000000000277

McCarty, T. R., Chouairi, F., Hathorn, K. E., Chan, W. W., & Thompson, C. C. (2022). Trends and Socioeconomic Health Outcomes of Cannabis Use Among Patients with Gastroparesis: A United States Nationwide Inpatient Sample Analysis. *Journal of clinical gastroenterology*, *56*(4), 324–330. https://doi.org/10.1097/MCG.0000000000001526

Parkman, H. P., Sharkey, E. P., Nguyen, L. A., Yates, K. P., Abell, T. L., Hasler, W. L., Snape, W., Clarke, J., Schey, R., Koch, K. L., Kuo, B., McCallum, R. W., Sarosiek, I., Grover, M., Farrugia, G., Tonascia, J., Pasricha, P. J., & Frank A. Hamilton for the NIH Gastroparesis Consortium (2020). Marijuana Use in Patients with Symptoms of Gastroparesis: Prevalence, Patient Characteristics, and Perceived Benefit. *Digestive diseases and sciences*, *65*(8), 2311–2320. https://doi.org/10.1007/s10620-019-05963-2

Pittayanon, R., Yuan, Y., Bollegala, N. P., Khanna, R., Lacy, B. E., Andrews, C. N., Leontiadis, G. I., & Moayyedi, P. (2019). Prokinetics for Functional Dyspepsia: A Systematic Review and Meta-Analysis of Randomized Control Trials. *The American journal of gastroenterology*, *114*(2), 233–243. https://doi.org/10.1038/s41395-018-0258-6

U.S. Department of Health and Human Services (n.d.). *Gastroparesis*. National Institute of Diabetes and Digestive and Kidney Diseases. Retrieved September 1, 2022, from https://www.niddk.nih.gov/health-information/digestive-diseases/gastroparesis

Ye, Y., Jiang, B., Manne, S., Moses, P. L., Almansa, C., Bennett, D., Dolin, P., & Ford, A. C. (2021). Epidemiology and outcomes of gastroparesis, as documented in general practice records, in the United Kingdom. *Gut*, *70*(4), 644–653. https://doi.org/10.1136/gutjnl-2020-321277

Zheng, T., & Camilleri, M. (2021). Management of Gastroparesis. *Gastroenterology & hepatology*, *17*(11), 515–525.

Minnesota Department of Health
Office of Medical Cannabis
PO Box 64882
St. Paul, MN 55164-0882
651-201-5598
health.cannabis@state.mn.us
www.health.state.mn.us

10/06/2022

To obtain this information in a different format, call: 651-201-5598. Printed on recycled paper.