**Cannabis-Based Medicines in Gastroparesis and Related Syndromes**

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## ABSTRACT

**Background:** Gastroparesis (GP) is a debilitating disorder characterized by delayed gastric emptying and symptoms such as nausea, vomiting, and abdominal pain, which significantly impact quality of life and healthcare costs. Current FDA-approved therapies, primarily metoclopramide, offer modest efficacy and carry a high burden of side effects, leaving many patients with inadequately controlled symptoms. While emerging data suggest that cannabis-based medicines (CBMs) may provide symptomatic relief, their safety profile, efficacy, and the quality of supporting evidence remain poorly characterized.

**Goals:** To systematically evaluate the safety and efficacy of cannabis-based medicines (CBMs) and endocannabinoid system modulation in patients with gastroparesis and related syndromes.

**Methods:** We systematically reviewed evidence regarding the safety and efficacy of cannabis in the treatment of gastroparesis (GP) and related syndromes. We searched 6 electronic databases using search terms related to cannabis-based medicines (CBMs), the endocannabinoid system (ECS), gastroparesis, and functional dyspepsia (FD). 2538 articles were identified and screened, of which 38 articles were included.

**Results:** Women with diabetic gastroparesis (GP) demonstrated significantly reduced plasma levels of endocannabinoids anandamide (AEA) and 2-arachidonoyl glycerol (2-AG) compared to diabetic controls (P- values for both not specified in text). In the first randomized controlled trial of pharmaceutical CBD for GP, treatment significantly reduced total Gastroparesis Cardinal Symptom Index (GCSI) scores (P=0.008), vomiting episodes (P=0.006), and overall symptom severity (P=0.03), despite paradoxically slowing gastric emptying. Cross-sectional data indicated that 93.5% of patients perceived symptom improvement with marijuana, which was significantly more effective than synthetic dronabinol (91% vs 47%; P<0.01). Large-scale retrospective analyses showed that cannabis use in GP inpatients was independently associated with lower inpatient mortality (aOR: 0.45; 95% CI: 0.33-0.60; P<0.001) and significantly lower hospitalization costs (P<0.001). However, recent propensity-matched data associated cannabis use with increased odds of emergency department visits (aOR: 1.53) and hospitalizations (aOR: 1.55; 95% CI: 1.49-1.61). Adverse associations include a potential link between cannabis and recurrent diabetic ketoacidosis in diabetic GP populations and a preliminary correlation between concurrent cannabis/semaglutide use and higher GP incidence.

**Conclusion:** Evidence is limited and of moderate quality, but suggests three preliminary interpretations: 1. Dysregulation of the endocannabinoid system may be associated with gastroparesis-related syndromes (GPRS), which may potentially be managed by adjusting intake of exogenous cannabinoids. 2. Many patients perceive relief of gastroparetic symptoms with cannabis-based medicine, but use is also associated with more severe symptoms. 3. Cannabis use in GP is associated with lower inpatient morbidity, mortality, and total inpatient healthcare costs, although rates of emergency department utilization is conflicting. These first three observations support the argument that CBM's can be useful and safe in the treatment of gastroparesis. More research is needed to identify confidently which associated phenotypes, genotypes, and comorbidities of gastroparesis are likely to respond positively to CBM.