**Title**: A comparison of haloperidol 5mg IM vs droperidol 2.5mg and ondansetron for the treatment of hyperemesis in cyclic vomiting syndrome

**NCT#:** NCT05065567

**Date:** 5/19/2025

**Introduction or Background**: Over the past 5 years there has been a 609% increase in persistent vomiting (cyclic vomiting syndrome) related hospitalizations. Many of these have been associated with cannabis use. Despite this significant increase in frequency there is scant literature on the most effective treatment of this condition. A variety of acceptable treatments include ondansetron (Zofran), haloperidol (Haldol) and droperidol. A recent study by Ruberto et al found haloperidol superior to odansteron for treatment of this condition. Droperidol, a similar D2 agent like haloperidol has been widely used as another treatment option for cyclic vomiting. To date, the two agents have not been compared to determine superiority in managing the symptoms related to cyclic vomiting.

**Problem and Purpose Statement**- The purpose of this study is to compare two commonly used agents for the treatment of cyclic vomiting to see if one agent is inferior to the other in time to improvement in symptoms, need for repeat or rescue medications, treatment failures and complications/side effects. To date, no head to head studies have been published with these two agents.

Research Questions or Hypothesis: Is droperidol or haloperidol inferior to the other agent in reducing symptoms related to cyclic vomiting.

**Theoretical Framework-Present Knowledge:** In a recent head to head study, Ruberto et al found that Haloperidol was superior to ondansetron (difference 2.3 cm [95% confidence interval 0.6 to 4.0 cm]; P=.01), with similar improvements in both pain and nausea, as well as less use of rescue antiemetics (31% versus 59%; difference -28% [95% confidence interval -61% to 13%]) and shorter time to emergency department (ED) departure (3.1 hours [SD 1.7] versus 5.6 hours [SD 4.5]; difference 2.5 hours [95% confidence interval 0.1 to 5.0 hours]; P=.03). Haldol, a D2 receptor antagonist, is thought to help suppress the nausea centers of the brain and reduce symptoms from cyclic vomiting. Droperidol, also a D2 antagonist is theorized to have a similar effect. Droperidol has been noted to possibly have a faster time of onset than haloperidol and droperidol is routinely used IV while haloperidol is typically a IM injection.

Literature Review:

Outlines the increase frequency of cyclic vomiting and the need for better treatment. Patel, Rikinkumar S., et al. "Burden of Persistent Vomiting With Cannabis Use Disorder: Report From55,549 Hospitalizations in the United States." Psychosomatics 60.6 (2019): 549-555.

Outlines the association of cyclic vomiting and cannabis as well as common treatments in the ED including haloperidol and droperidol

Kim, Howard S., et al. "Cyclic vomiting presentations following marijuana liberalization in Colorado." *Academic Emergency Medicine* 22.6 (2015): 694-699.

Outlines the pharmokenetics for treatment of cyclic vomiting

Bashashati, Mohammad, and Richard W. McCallum. "Neurochemical mechanisms and pharmacologic strategies in managing nausea and vomiting related to cyclic vomiting syndrome and other gastrointestinal disorders." *European Journal of Pharmacology* 722 (2014): 79-94.

Retrospective study on the effect of droperidol in treating cyclic vomiting

Lee, Carl, Shaun L. Greene, and Anselm Wong. "The utility of droperidol in the treatment of cannabinoid hyperemesis syndrome." *Clinical Toxicology* 57.9 (2019): 773-777.

Treatment options for cyclic vomiting

Richards, John R. "Cannabinoid hyperemesis syndrome: pathophysiology and treatment in the emergency department." The Journal of emergency medicine 54.3 (2018): 354-363.

Valdovinos, Erica M., et al. "A Nonopioid, Nonbenzodiazepine Treatment Approach for Intractable Nausea and Vomiting in the Emergency Department." Journal of Clinical Gastroenterology 54.4 (2020): 327-332.

Comparison for haloperidol to ondansetron for treatment of cyclic vomiting

Ruberto, Aaron J., et al. "Intravenous Haloperidol Versus Ondansetron for Cannabis Hyperemesis Syndrome (HaVOC): A Randomized, Controlled Trial." *Annals of Emergency Medicine* (2020).

**Methodology**:

This is a clinical trial that will enroll approximately 100 subjects from three different research sites. Patients who have been diagnosed with cyclic vomiting syndrome and enrolled in our study will be given standard treatment of 2.5mg droperidol IV, 8mg ondansetron IV or 5mg haloperidol IM per physician's choice. The research specialist will be notified when the drugs are administered and view the patient's chart to determine if the reason for the anti-nausea drug was a diagnosis of cyclic vomiting syndrome. If so, the patient's nurse will be messaged via EPIC to inquire on the patient's pain and nausea scores initially versus two hours after the drug is administered, if at the St. Joseph ED, research specialist will make contact with the patient and ask pain/nausea scores at baseline and 2 hours later themselves.

Inclusion criteria will be adult patients with a clinical diagnosis of cyclic vomiting in the ED

Exclusion criteria would include pregnancy, allergy to any of the study medicines

Primary outcome will be change in pain and nausea at 2 hrs using a visual analog scale of 0-10

Secondary outcome will be:

1. Change in pain [ Time Frame: 1, 2, 24 and 48 hours ]

   Changes in abdominal pain score at 1, 2, 24 and 48 hours vs. baseline

2. Change in nausea [ Time Frame: 1, 2, 24 and 48 hours ]

   Changes in nausea score at 1, 2, 24 and 48 hours vs. baseline

3. Treatment success [ Time Frame: 2, 24 and 48 hours ]

   Treatment success = both abdominal pain and nausea score < 2 at 2, 24 and 48 hours

4. Discharge ready at 2 hours [ Time Frame: 2 hours ]

   Deemed discharge-ready at 2 hours in the opinion of the treating physician

5. Rescue anti-emetics in ED [ Time Frame: at discharge from Emergency Department or 12 hours whichever comes first ]

   Given rescue anti-emetics prior to discharge

6. Time to discharge from ED [ Time Frame: at discharge from Emergency Department or 12 hours whichever comes first ]

   Time interval to discharge-ready from t=0 (min)

   Subject preferred Time to Discharge from ED" > 12 hours (binary yes/no)

7. Return to ED [ Time Frame: 7 days ]

   Unscheduled return visits to ED within 7 days (count)

8. Prolonged ED Length of stay [ Time Frame: at discharge from Emergency Department or 12 hours whichever comes first ]

   Outcome 10 "

**Research Design**:

Patients presenting with a chief complaint of vomiting and abdominal pain will be screened by the bedside provider for the diagnosis of cyclic vomiting or cannabis induced vomiting syndrome. Per the doctor's choice, 2.5mg droperidol, 5mg haloperidol or 8mg odansteron will be administered. The remaining portion of the patients care is at the discretion of the treating provider including the use of fluids, laboratory diagnostics and radiographic diagnosis and pain medications. The research specialist will be notified when the drugs are administered and view the patient's chart to determine if the reason for the anti-nausea drug was a diagnosis of cyclic vomiting syndrome. If so, the patient's nurse will be messaged via EPIC to inquire on the patient's pain and nausea scores initially versus two hours after the drug is administered, if at the St. Joseph ED, research specialist will make contact with the patient and ask pain/nausea scores at baseline and 2 hours later themselves. Our research specialist will contact patients 1 and 2 days following treatment and enter responses into the project spreadsheet housed on Spectrum Health Lakeland servers. The provider may, at any time choose to add additional anti emetics at their choice but this will be considered as a "rescue" medication for the purposes of this study. All enrolled patients will be added to a study list where the medication given as well as the the secondary outcomes will be recorded on a secure spreadsheet for analysis later.

Continuous variables (such as pain and nausea score, length of stay in the ED will be analyzed using 2 tailed student t-tests. Qualitative variables (number with 2 point improvement in abd pain and nausea score, discharge state at 2 hours, need for rescue anti-emetic, return to ED) will be analyzed using chi-squared analysis.

**Ethical Considerations**:

Risks (current and potential).: As all three are standard care the risks are limited to the usual risks associated with treating this condition to include standard medicine reactions, somnolence and dystonic reaction (known with D2 antagonists) and possible QT prolongation (known in all 3 medications). Patients will receive standard care for any side effects of medicine as per standard practice of Emergency Medicine.

**Potential benefits** to the group or class from which the subjects are recruited. Potential benefits to society.

Droperidol has not been commonly used in our emergency departments in the past and if this medicine works better than the others then these patients could experience decreased length of stay and improved time to improvement of symptoms. It is our hope that this project could help guide treatment for this group of patients in the future.

The risk/benefit ratio remains the same whether patients are participating in this study or not. Our clinicians would be using these medicines to treat cyclic vomiting. By formally evaluating response we hope to provide better feedback to physicians going forward with regard to the relative utility of these medicines

**Informed consent**

Patients experiencing cyclical vomiting exacerbations tend to be very symptomatic and are very uncomfortable. The HAVOC trial (Ruberto et al) experienced low enrollment due to patients not being able to participate in consent discussions. The medicines we are proposing to use are all medicines that have been effective for cyclic vomiting, but it is unknown if droperidol, a relatively recent re-addition to clinicians' pharmacologic armamentarium is better or worse than haloperidol. We feel that since clinicians are going to try droperidol for these patients anyway, we would like to formally assess its utility. We do not want to delay these patients' treatment to go over a lengthy consent document for medicines that will frequently be used in any case, and these patients will often not tolerate carrying this discussion out

**Statistical Analyses:** Means and standard deviations were reported for baseline pain and nausea and for pain and nausea after 2 hours of drug administration for the three arms of the study. ANOVAs were conducted to determine whether significant differences existed between baseline and 2 hours after drug administration for the three drugs. Due to low response rate at 24 and 48 hours (6 pts), these time points were not included in the analysis.

References:

Outlines the increase frequency of cyclic vomiting and the need for better treatment. Patel, Rikinkumar S., et al. "Burden of Persistent Vomiting With Cannabis Use Disorder: Report From55,549 Hospitalizations in the United States." Psychosomatics 60.6 (2019): 549-555.

Kim, Howard S., et al. "Cyclic vomiting presentations following marijuana liberalization in Colorado." *Academic Emergency Medicine* 22.6 (2015): 694-699.

Bashashati, Mohammad, and Richard W. McCallum. "Neurochemical mechanisms and pharmacologic strategies in managing nausea and vomiting related to cyclic vomiting syndrome and other gastrointestinal disorders." *European Journal of Pharmacology* 722 (2014): 79-94.

Lee, Carl, Shaun L. Greene, and Anselm Wong. "The utility of droperidol in the treatment of cannabinoid hyperemesis syndrome." *Clinical Toxicology* 57.9 (2019): 773-777.

Richards, John R. "Cannabinoid hyperemesis syndrome: pathophysiology and treatment in the emergency department." The Journal of emergency medicine 54.3 (2018): 354-363.

Valdovinos, Erica M., et al. "A Nonopioid, Nonbenzodiazepine Treatment Approach for Intractable Nausea and Vomiting in the Emergency Department." Journal of Clinical Gastroenterology 54.4 (2020): 327-332.

Ruberto, Aaron J., et al. "Intravenous Haloperidol Versus Ondansetron for Cannabis Hyperemesis Syndrome (HaVOC): A Randomized, Controlled Trial." *Annals of Emergency Medicine* (2020).