Title

A Pilot Study on the Efficacy and Safety of Olanzapine in Improving Symptoms and Gastric Motility in Gastroparesis

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SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations.

Site Investigator:*

Signed: _____ Date: _____

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** The protocol should be signed by the clinical site investigator who is responsible for the day to day study implementation at his/her specific clinical site.*

LIST OF ABBREVIATIONS

GI, Gastrointestinal
TD, Tardive dyskinesia
BMI, Body mass index
5-HT, 5-hydroxytryptamine
GCSI-DD, Gastroparesis cardinal symptom index-daily diary
VAS, Visual analog scale
BSFS, Bristol stool form scale
Hgb A1c, Hemoglobin A1c
TSH, Thyroid stimulating hormone
WMC, Wireless motility capsule
EPS, Extrapyramidal side-effects
CMP, Comprehensive metabolic panel
EKG, Electrocardiogram

1 BACKGROUND/SCIENTIFIC RATIONALE

Gastroparesis is a disorder characterized by impaired gastric emptying in the absence of obstruction of the proximal gastrointestinal (GI) tract. Symptoms typically include postprandial fullness, nausea, vomiting, bloating, and pain. In severe cases, anorexia and weight loss may be present. It is estimated to affect up to 5 million persons in the US with an age-adjusted prevalence of 37.8 per 100,000 persons [1]. The most common identifiable etiology is diabetes mellitus in 30% but 36% are classified as idiopathic [2]. Gastroparesis is a chronic disabling condition that is associated with a significantly worse outcome compared to age and sex matched controls [3].

Currently, the only FDA approved medication for treatment of gastroparesis is metoclopramide. Recently, metoclopramide was issued a black box warning by the FDA because of the risk of adverse events, especially tardive dyskinesia, a potentially irreversible neurologic condition characterized by uncontrollable facial, oral, and lingual movements. National guidelines suggest the risk of developing tardive dyskinea is 1-15% [4, 5]. Although the actual risk of TD may be much lower, the evidence supporting the use of metoclopramide in gastroparesis is fairly weak, it may not alleviate symptoms of anorexia and weight loss, and development of other agents with better efficacy and less adverse effects is needed [6].

Macrolide antibiotics have also been used in the treatment of gastroparesis. They act on motilin receptors to cause pro-motility effects but have no central effects on nausea, hunger, and appetite stimulation [7, 8]. In addition, tachyphylaxis may limit long-term use.

Olanzapine is a second generation anti-psychotic that is FDA approved for the treatment of schizophrenia and bipolar disorder. Second generation anti-psychotics typically have fewer extrapyramidal side effects (e.g. akathisia, dystonia, parkinsonian symptoms) as well as tardive dyskinesia compared to older anti-psychotics [9, 10]. However, they do carry potential for serious metabolic risk, specifically weight gain, hypertension, hyperlipidemia, and ultimately development of diabetes mellitus. Olanzapine has been associated with one of the highest risks of weight gain among atypical anti-psychotics [11, 12]. It is unclear if this is related to other actions or if it is related to attenuation of the disease process. Patients with schizophrenia may have a predisposition towards obesity with a prevalence of up to twice the general population [13]. Genetic predisposition, higher prevalence of smoking, and neuroendocrine changes associated with psychosis have all been postulated as possible contributing factors to increased obesity in schizophrenia and bipolar disorder [14-18].

Olanzapine may also have other therapeutic effects outside of controlling psychosis. Phase I and II studies have shown olanzapine significantly relieves nausea and emesis in a palliative care setting [19-21]. It was found to be safe in both trials and helped stimulate appetite and augment weight gain. There is also evidence that olanzapine may be beneficial in the

treatment of eating disorders. Several double blind, placebo-controlled trials have shown benefit of olanzapine in terms of attaining goal BMI and improving psychological measures [22-24]. Furthermore, the medication was well tolerated in this population without development of adverse metabolic events [22, 23, 25].

Olanzapine has actions at multiple receptors throughout the body, which may make it a unique drug for the treatment of gastroparesis. These include antagonism of dopamine, serotonin, $alpha_1$ adrenergic, muscarinic, and histamine receptors [26, 27]. Many of these receptors, especially D_2 and $5HT_3$, are involved in the signaling of nausea and emesis [28]. As a result, olanzapine may have anti-nausea properties that could be utilized in gastroparesis. Antagonism of D_2 receptors may also provide motor effects in the stomach, as this is one of the main mechanisms of action for metoclopramide [29-31].

Furthermore, olanzapine may also have effects on gut neurohumoral signaling that are important in regulation of appetite and weight. Long-term use of olanzapine between 26 and 52 weeks has been shown to increase plasma levels of ghrelin in mouse models as well as humans on long-term treatment for schizophrenia [32-34]. However, short-term use between 2 to 9 weeks may actually decrease levels of ghrelin [35-37]. Ghrelin is a hormone that is produced by the gut, stimulates appetite, and has been shown to improve symptoms as well as promote gut motility in gastroparesis [38-40]. Previous data have shown that olanzapine may affect only ghrelin levels whereas other gut hormones, e.g. peptide YY, pancreatic polypeptide, leptin and GLP-1 were not affected [34, 37]. Because of this data as well as limited resources, only ghrelin is going to be evaluated during this study.

There are few options currently that are efficacious and safe for the treatment of gastroparesis and development of other therapeutic options is needed. Furthermore, in patients with severe gastroparesis causing anorexia and weight loss, polypharmacy is often needed to stimulate appetite and alleviate symptoms. Olanzapine may possess unique properties, which makes it a potentially attractive therapeutic option for gastroparesis. We hypothesize that olanzapine will be effective and safe in controlling symptoms as well as stimulate appetite in gastroparesis. We also hypothesize that olanzapine will promote gastric motility. Finally, we hypothesize that olanzapine will stimulate the secretion of ghrelin, thereby aiding in the treatment of gastroparesis. This pilot study may provide further insight into the efficacy and safety of olanzapine in gastroparesis, which could be utilized in a larger randomized, placebo-controlled prospective study in the future.

2 OBJECTIVES

Aim 1: Investigate the efficacy and safety of olanzapine in the treatment of non-diabetic gastroparesis.

We will utilize the gastroparesis cardinal symptom index daily diary (GCSI-DD) and an appetite visual analog scale (VAS) to compare severity of symptoms before and after treatment with olanzapine. Subjects will undergo regular testing of blood glucose, insulin, hemoglobin (Hgb) A1c, body mass index (BMI), liver enzymes, thyroid stimulating hormone (TSH), and prolactin levels during the study as well as after treatment completion to determine the safety of the medication. All adverse events will be compiled to investigate the tolerability of the medication.

Aim 2: Determine whether olanzapine has prokinetic effects on gastric emptying in gastroparesis.
We aim to test gastric motility, including gastric emptying and antroduodenal contractility parameters, by wireless motility capsule (WMC) before and at the completion of the study to determine if olanzapine has any pro-motility effects in gastroparesis.

Aim 3: Examine the effects of olanzapine on neurohumoral regulation of eating and appetite.
We seek to determine whether olanzapine promotes secretion of ghrelin in gastroparesis.

3 EXPECTED RISKS/BENEFITS

The data accumulated in this study will advance our understanding of the pathophysiology of gastroparesis, and may provide important information on whether olanzapine is helpful in the treatment of idiopathic gastroparesis.

There are potential direct benefits for all gastroparesis subjects in this study. On study entry, physiologic tests of gut function and motility will be performed that may provide new insight into causes of symptoms in patients with IBS. In addition, all subjects will be seen by the PI and/or study team frequently during the study. Adverse events, vital signs, and laboratory parameters will be assessed to monitor overall safety and tolerability of the medication. Survey information will also be obtained using validated questionnaires including GCSI-DD, appetite VAS, and BSFS. The GCSI-DD is a validated questionnaire composed of twelve questions that takes approximately 10 minutes to complete. The appetite VAS is a single item questionnaire that tracks changes in appetite over time. This will take approximately 1 minute to complete. The BSFS is a questionnaire that allows researchers and subjects track changes in bowel form and frequency. This will take approximately 1 minute to complete. This frequent and comprehensive assessment provided as part of participating in this study may allow for closer monitoring of disease course.

There are potential risks for subjects, including:

1. Olanzapine Risks:

Weight gain: Weight gain is a known risk when patients with schizophrenia or other psychiatric illnesses are taking olanzapine. This may also predispose the patient to develop underlying obesity, hyperlipidemia, diabetes mellitus, and coronary artery disease. However, this may be a risk inherent to this specific population and may not be applicable to the general population. Human studies in patients with anorexia nervosa and other eating disorders have shown the safety and tolerability of olanzapine. We will exclude anyone with a history of diabetes mellitus or hyperglycemia. We will also monitor the subjects closely during the study period and anyone who exhibits hyperglycemia (fasting glucose > 150 mg/dl or non-fasting glucose > 180 mg/dl), and/or rapid weight gain (> or = 5 kgs/week) will be taken off the study drug. Subjects will continue to be monitored for 14 days after completion of the study drug.

Orthostatic hypotension: Subjects who are taking concomitant anti-hypertensive medications will be warned about the risk of potentiating orthostatic hypotension with olanzapine. They will be asked to exercise caution especially when changing positions suddenly.

Hyperglycemia: Subjects will be given a handout at the start of the trial discussing potential symptoms of hyperglycemia, including excessive thirst, frequent urination, blurry vision, and fatigue. Subjects will be asked to notify the study coordinator immediately if they have any of these symptoms.

Somnolence: Subjects will be asked to take the olanzapine at bedtime to minimize the effects.

Constipation: Subjects will be instructed on potential effects of olanzapine on bowel habits and may take laxatives to help with constipation.

Olanzapine appears to be well tolerated in placebo-controlled trials. The only adverse events occurring more frequently with olanzapine compared with placebo were somnolence, constipation, and weight gain. However, other adverse events have been reported in the literature and will be listed below.

Extrapyramidal side-effects: Animal models as well as human studies have shown low potential for olanzapine to cause extrapyramidal side-effects (EPS), such as parkinsonism, akathisia, and dystonia. Subjects will be monitored during the study period for development of EPS.

Thyroid dysfunction: There is a small risk for causing thyroid dysfunction. Thyroid levels will be checked as part of the screening period and patients with underlying dysfunction will be excluded from the study. If thyroid dysfunction occurs during the study, they will have the option of withdrawing from the study.

Hyperprolactinemia: Olanzapine produces minimal effects on prolactin levels in patients with schizophrenia. This will also be monitored prior to starting the study drug and subjects with abnormal levels of prolactin will be excluded. Patients who exhibit signs and symptoms of hyperprolactinemia during the study period will be given the option of withdrawing from the study.

Seizures: Lowering of the seizure threshold has been seen in subjects taking olanzapine. This may be a dose-dependent response and certain factors including younger age, female sex, and concomitant SSRI use causes higher serum levels of olanzapine. We intend to use a small dose of olanzapine and will exclude subjects with a history of seizure disorder.

LFT abnormalities: Olanzapine can occasionally cause elevations in levels of hepatic transaminases. However, the elevations appear to be transient and no evidence of hepatotoxicity has been reported.

Hematologic abnormalities: There are no reports of agranulocytosis with olanzapine, even in those who previously had experienced olanzapine-induced dyscrasias.

2. Wireless Motility Capsule Risks:

WMC may become stuck in the intestines and rarely requires surgery to relieve an obstruction. There is also a small possibility that WMC may interfere with a pacemaker or defibrillator.

3. Blood Draw Risks

Risks of blood draw include pain, bruising, irritation, or redness at the site where the blood will be drawn. An infection at the site of the blood draw is possible. Subjects could become faint.

4. Childbearing Risks

The study drug may cause harm to an unborn child or nursing infant, and for this reason, no subject may be breast-feeding, pregnant, or plan to become pregnant.

5. Electrocardiogram (EKG) Risks

An electrocardiogram (EKG) involves placing electrodes on the chest wall. There may be some soreness in removing the electrodes and patients may develop a rash where the electrodes are attached.

6. Risks to Privacy

There is a potential risk to the subject's privacy. While every effort will be made to maintain privacy, it is possible that others may learn about information acquired from the medical records. Such a breach might lead to problems with getting insurance or a job.

7. General risks

This is an interventional study. Subjects' condition may worsen or improve while undergoing intervention with olanzapine. Participation in this study will not prevent normal clinical care of gastroparesis or its consequences. In addition, some prescribed medications may need to be stopped temporarily during the study. Subjects will also be asked to hold any medications that may potential influence GI motility or appetite within one week prior to starting and for the duration of the study, including prokinetic drugs, macrolide antibiotics (erythromycin), opioid pain medications, GLP-1 mimetics. If subjects are taking any of these medications, their symptoms may return or worsen when they are stopped. However, the stopping of medications is temporary and is not felt to cause any undue hardship. Finally, there is a risk that some of the questions in the surveys may produce emotional distress. If the subject desires, he/she can be referred to a mental health specialist within the UMHS or another provider outside the UMHS system.

4 ELIGIBILITY CRITERIA

Inclusion Criteria:

- Male or female between 18 and 80 years of age, inclusive.
- Has gastroparesis at screening (gastric half-time of emptying > upper limit of normal as determined by wireless motility capsule)
- Must have a > or = 6 month history of relevant symptoms of gastroparesis, (e.g., chronic post-prandial fullness, early satiety, postprandial nausea), patients will have a mean of the daily scores over a minimum of 7 days indicating > or = mild (2) assessed using the GCSI-DD during the screening period prior to randomization.
- A female subject is eligible to participate if she is of non-childbearing potential or child-bearing potential and agrees to use one of the approved contraception methods. Female patients must agree to use contraception for at least 5 days following the last dose of study medication.

- Male subject must agree to use of contraception. Contraception must be followed from the time of the first dose of study medication through at least 5 days after the last dose of study medication.
- BMI ≥ 18 and < 30 kg/m2 (inclusive).
- Subjects on anti-hypertensive medications may be allowed to participate but should exercise caution given risk of orthostatic hypotension
- Subject has never had a gastrectomy, nor major gastric surgical procedure or any evidence of bowel obstruction or strictures within the previous 12 months
- Dosage of any concomitant medications has been stable for at least 3 weeks.
- Estimated (or measured) glomerular filtration rate ≥ 30 mL/min.
- QTcB or QTcF < 450 msec or QTc < 480 msec in patients with Bundle Branch Block based on single or average QTc value of triplicate values obtained over a brief recording period.
- Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.
- AST and ALT < 2xULN; alkaline phosphatase and bilirubin ≤ 1.5xULN; normal CBC, TSH, and prolactin levels.

Exclusion Criteria:

- Subject has a history of diabetes mellitus, hyperglycemia, hyperlipidemia, cardiovascular disease, cerebrovascular disease, seizures, hyperprolactinemia, Parkinson's disease, or dementia.
- Subject has a history of elevated glucose level (fasting blood glucose level of 100-126 mg/dl and/or non-fasting glucose level of 140-200 mg/dl)
- Subject has history of underlying schizophrenia, bipolar disorder, suicidal ideation/attempt, or has used olanzapine in the past.
- Subjects with a pacemaker and/or defibrillator
- Subject has acute severe gastroenteritis
- Subject has a gastric pacemaker
- Previous gastric surgeries
- Subject is on chronic enteral (e.g., feeding tube) or parenteral feeding
- Subject has pronounced dehydration
- Subject has evidence of severe cardiovascular autonomic neuropathy (e.g. history of recurrent syncope in the last 6 months)
- Subject has a history of eating disorders (anorexia nervosa, binge eating, bulimia)
- Use of medications potentially influencing upper gastrointestinal motility or appetite within one week of the study (e.g., prokinetic drugs, macrolide antibiotics (erythromycin), GLP-1 mimetics)
- Regular opiate use
- Subjects who are taking drugs that potentially interact with olanzapine including diazepam, lorazepam, alcohol, carbamazepine, fluvoxamine, olanzapine and

fluoxetine in combination, CNS acting drugs, levodopa and dopamine agonist, and olanzapine when used in combination with lithium or valproate
- History or presence of clinically significant gastro-intestinal, hepatic or renal disease or other condition that would in the opinion of the investigator or medical monitor make the subject unsuitable for inclusion in this clinical study.
- The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
- History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator would make the subject unsuitable for inclusion in this clinical study
- Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56 day time-period.
- Pregnant females as determined by positive serum or urine hCG test (from the first urine of the day) at screening or prior to dosing.
- Lactating females.
- Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
- Subject has a history of dysphagia.
- Subject has had intrapyloric botox injections within the past 6 months.

5 SUBJECT ENROLLMENT

Most patients with gastroparesis are seen in gastroenterology or general medicine clinics. Patients will be recruited from gastroenterology and general medicine clinics at Taubman Center and in the satellite clinics within the University of Michigan Health System. Eligible subjects will be contacted and given material explaining the nature of the study, including information related to wireless motility testing and introduction to olanzapine. They will be given time to read the materials. If they choose to participate, they will sign the consent document in the presence of the PI and/or Designee. Subjects will be enrolled on a first come, first served basis. This approach will ensure that subjects are representative of the population of patients with gastroparesis in Southeast Michigan.

Emails to providers in the General Medicine and Gastroenterology clinics in the University of Michigan System, public advertisements, and telephone calls will be utilized to recruit subjects.

Subjects who do not meet inclusion/exclusion criteria will not be enrolled in the study. All data collected from subjects who are screen failures will be saved for data analysis.

6 STUDY DESIGN AND PROCEDURES

This is a pilot study of 10 consecutive subjects ages 18 – 80 with documented delayed gastric emptying within the past 2 years and history of nausea, vomiting, bloating, anorexia, early satiation, post-prandial fullness, and weight loss for at least 6 months without structural or organic cause will be enrolled. This will be an open label trial without a placebo arm to determine efficacy and safety of the medication in this population. This will be a single center study with subjects being enrolled at the University of Michigan. Dr. Braden Kuo at Massachusetts General Hospital will act as a co-I and will assist with data analysis but will not enroll any patients. Dr. Kuo will receive only de-identified information.

The study will consist of a screening/baseline period of up to 30 days, an 8-week treatment period, and a 14-day post treatment safety follow-up visit and assessment of symptoms.

Screening/Baseline:
Subjects will participate in a screening/baseline visit within 30 days prior to study dosing. Subjects will be instructed to fast prior to the screening visit at which time they will undergo blood sampling for complete blood count (CBC), complete metabolic panel (CMP), lipid profile, insulin, Hgb A1c, prolactin, TSH, and urine or blood pregnancy screen (if applicable). A baseline ECG will also be performed. Ghrelin levels will be measured. Baseline vital signs, height, weight, and BMI will also be calculated. They will also have their gastric emptying assessed by wireless motility capsule (WMC). To be eligible for the study, the subjects' gastric emptying time, as determined by WMC, needs to be greater than 5 hours. Potential subjects will complete the gastroparesis cardinal symptom index daily diary (GCSI-DD) evaluation, appetite visual analog score (VAS), and Bristol Stool Form Scale (BSFS) for a minimum of 7 days to determine baseline level of symptoms [41]. Questionnaires will be completed in the evening after dinner. Mean total GCSI-DD score must be ≥ 2 in order to qualify for the study.

Week 1 – Week 8:
Subjects will initially start on olanzapine 2.5 mg by mouth daily to be taken at bedtime. Subjects will return on days 7 and 14 to determine response to medication. Medication dose can be increased to 5 mg on day 7 and 10 mg on day 14, respectively, based on incomplete symptom response, which is defined as a mean change in GCSI-DD score < 0.5 from baseline. Height and weight will be measured on Day 7. The total dose of olanzapine will not exceed 10 mg daily during this study.

Subjects will be monitored for adverse events and undergo blood sampling for glucose, insulin, and Hgb A1c on day 14. Vital signs, height, weight, and BMI will also be evaluated. Subjects will be instructed to bring their study medication with them on day 14 for assessment of study drug accountability.

Subjects will be contacted by phone at least once within 2 weeks following the day 14 visit to assess for potential side effects. Subjects may also come in for an extra/optional study visit between the Day 14 and Day 35 visits, if warranted by side effects.

Subjects will return on day 35 to monitor for adverse events, vital signs, height, weight, BMI, and glucose check.

During the study, subjects will rate their gastroparesis symptoms on a daily basis by completing the GCSI-DD and appetite VAS questionnaires. Subjects will also record daily the number of stools and their consistency [42]. Subjects will be asked to complete all diaries after the evening meal. The subjects will fast prior to returning to clinic on the morning of day 56 to undergo assessment of their gastric emptying time by WMC and complete an appetite VAS. Blood sampling for LFTs, glucose, insulin, Hgb A1c, and ghrelin levels will be performed. Vital signs, height, weight, and BMI will also be measured. All remaining study medication will be returned to the clinical unit for final drug accountability. Subjects will continue to rate their gastroparesis symptoms for 14 days following the end of dosing.

Adverse events, vital signs, and laboratory parameters will be assessed to monitor overall safety and tolerability of the medication. Common potential adverse effects of the medication include orthostatic hypotension, weight gain, hyperglycemia, hyperlipidemia, increased prolactin level, akathisia, somnolence, and tremor. Serious adverse effects include sudden cardiac death, diabetic coma, venous thromboembolism, cerebrovascular disease, seizure, and suicidal intent. A subject will be withdrawn from the study if they experience any serious adverse events or if they develop hyperglycemia (fasting glucose level > 150 mg/dl or non-fasting glucose level > 180 mg/dl), or weight gain (≥ 5 kg/wk). The FDA definition for serious adverse events (SAE) will be used which is defined as an AE resulting in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect related to the adverse event. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may

require medical or surgical intervention to prevent one of the outcomes listed in this definition. The PI will determine whether the SAE is related or possibly related to the drug. The trial will stop if any SAE related to the drug is encountered.
Subjects will be allowed to use ondansetron, promethazine, and/or prochlorperazine as rescue medications during the study. Laxatives, including Miralax, magnesium, Dulcolax, stool softeners, fiber supplements, and/or linaclotide may also be used during the study to treat underlying constipation. Subjects will not be allowed to use any prokinetic agents, such as Reglan, domperidone, or macrolide antibiotics (e.g. erythromycin) during the study. Rescue and concomitant medications (prescriptions or OTC medications) ongoing at the Screening Visit and/or started from the Screening Visit onwards until the last study related activity will be documented in the Prior and Concomitant Medication and Rescue medication pages of the Case Report Form (CRF). Subjects will be asked to monitor and record usage and frequency of rescue medications and laxatives used during the study.

Post-Treatment Assessment:
At the conclusion of 56 days of dosing, subjects will return for a follow-up visit 14 days (+ 2 days) after the last dose of study medication. All subjects will have blood sampling for CBC, CMP, lipid profile, TSH, prolactin, insulin, Hgb A1c, and ghrelin. Height, weight, and BMI will be calculated. One final appetite VAS will be completed. The duration of each patient's participation in the study from screening to follow-up visit will be approximately 14 weeks.

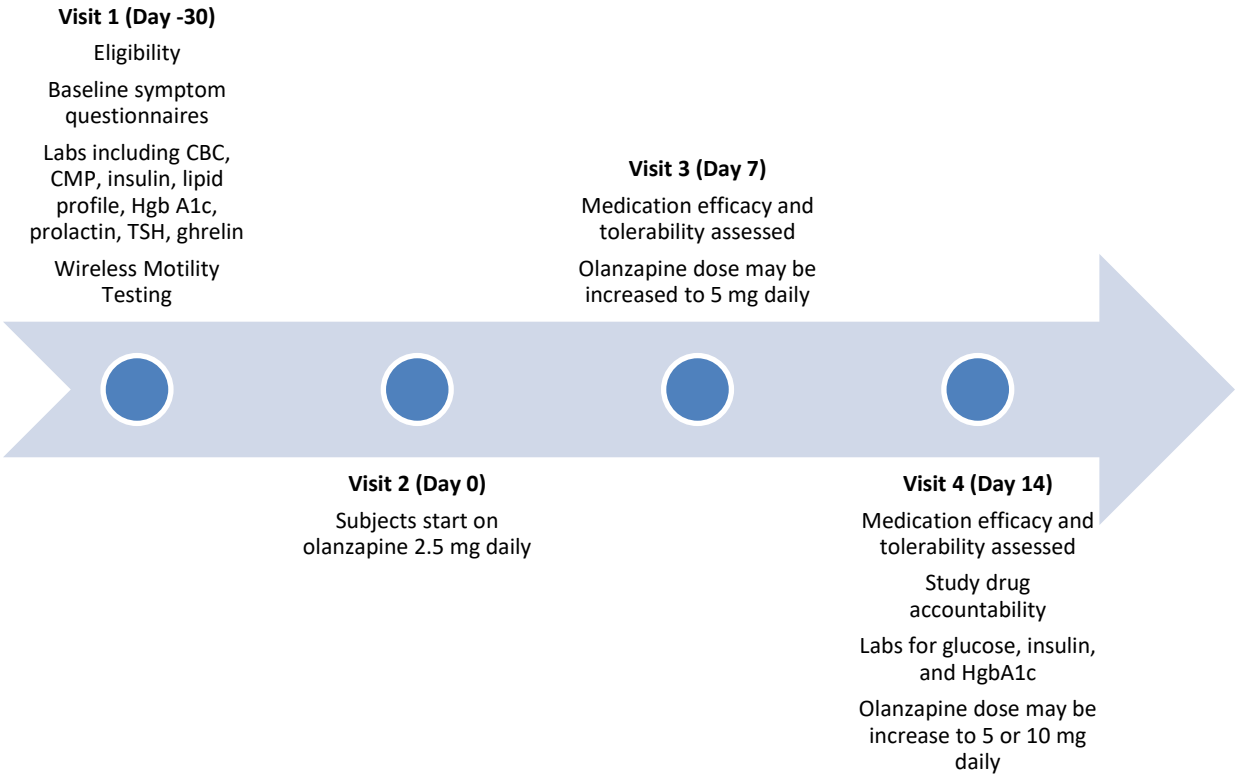
Subjects are free to discontinue participation in the study at any point. If a subject decides to prematurely discontinue from the study, they will be contacted within two weeks for safety follow-up visit(s). Reasons for withdrawal will be documented by the PI. If the reason for removal of a subject from the study is an AE, the principal specific event will be recorded on the CRF. The subject will be followed until the AE is resolved.

Gastric Motility:
Gastric motility will be tested by using the WMC wireless capsule system (The SmartPill Corporation, Buffalo, NY). This offers a potentially more complete examination into possible etiologies for gastroparesis including delayed gastric emptying as well as gastric and small bowel contractility abnormalities. We will follow the protocol for measuring gastric emptying by wireless motility capsule as described previously in the literature [43]. Gastric emptying time (GET) is defined as the duration of time from capsule ingestion to entry of the capsule into the duodenum. Subjects will swallow the WMC capsule with 50 ml of water followed by ingestion of a standardized meal comprising of a nutrient bar, which has a total caloric value of 255 kcal (72%

carbohydrate, 24% protein, 2% fat, and 2% fiber) [44]. Because of the low risk of capsule retention especially once the capsule enters the colon, plain abdominal radiograph (KUB) will be performed only if there is no documentation of the capsule passing the ileocecal valve and the patient has symptoms of capsule retention. Pressure data recorded by the WMC capsule will be analyzed for 1 hour before and after the WMC empties the stomach (GET). The analyzed parameters are: number of contractions (Ct), and motility index defined as: MI = Ln (sum of pressure amplitudes * number of contractions +1) [45].

Stopping Criteria:
The purpose of this study is to ensure that severe complications to olanzapine in gastroparesis are rare and to see whether olanzapine might improve symptoms in gastroparesis. We will treat ten patients with gastroparesis. The trial will stop if any SAE related to the drug is encountered.

Study Timeline:



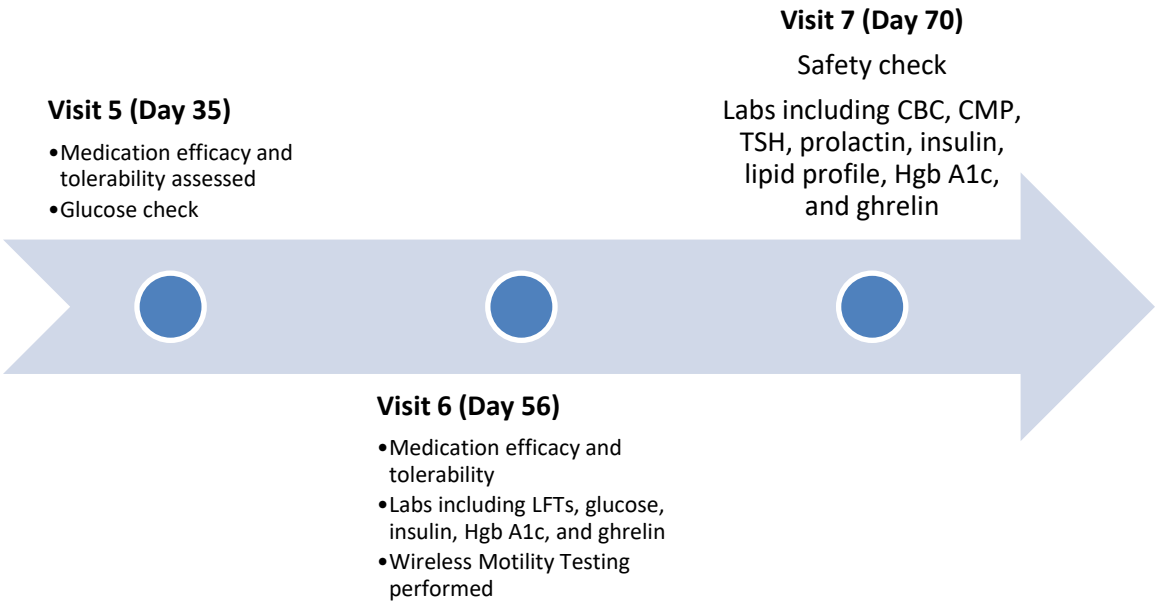


Figure 1 Gastroparesis Subject Timeline

7 Data Collection and Management Procedures

Data Handling and Entry: All data including questionnaire results and physiologic testing will be recorded and reviewed by the study team. Data will then be entered into an electronic case report form (eCRF) that complies with Title 21 of the Code of Federal Regulations (21 CFR Part 11). All passwords will be strictly confidential to protect subject's protected health information (PHI). Only the Primary Investigator (PI) and Study Coordinator will have access to the data and subject identifiers. Only the PI and Study Coordinator will be allowed to enter data onto the password-protected web-based server.

Computer Systems: Data entry will be entered into REDCAP which is validated and conforms to regulatory requirements. Only the Primary Investigator (PI) and Study Coordinator will have access to the data and subject identifiers. Only the PI and Study Coordinator will be allowed to enter data onto the password-protected web-based server.

Data Validation: Validation checks will be programmed within the eCRF system as well as supplemental validation performed by review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data.

Direct Access to Source Data: A developed review procedures that complies with Good Clinical Practice (GCP) guidelines.

Source Document/Case Report Form Completion: Source documents and the eCRFs will be completed for each study patient. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient's source document/eCRF. The source document/eCRF should indicate the patient's participation in the study and should document the dates and details of the study procedures, AEs, and patient status.

Record Retention: The Investigator will maintain all study records according to applicable regulatory requirement(s).

8 DATA ANALYSIS

Procedure for Accounting for Missing, Unused, and Spurious Data: The primary outcome measure in our study is whether olanzapine is efficacious and safe for the treatment of idiopathic gastroparesis. We will use multiple imputation with 10 imputed datasets to replace missing values on outcome and predictor variables [46]. If 10 imputed datasets are not sufficient to ensure stability of estimates, we will use 20 imputed datasets. This allows for maximal use of available data while maximizing statistical power.

9 QUALITY CONTROL AND QUALITY ASSURANCE

The PI and Study Coordinator will be responsible for Quality Control and Quality Assurance and will be performed in accordance with Standard Operating Procedures at the University of Michigan.

10 STATISTICAL CONSIDERATIONS

Changes in measures from baseline will first be examined using descriptive statistics and graphical analysis. Significance of changes by the post treatment assessment will be determined using paired t tests or Wilcoxon rank sum tests, depending on the normality of the measures. Hierarchical regression will be used to analyze patterns of change across all measurement times, with time as a nested factor within subject. Adverse events will be summarized by proportions and 95% confidence intervals.

Sample size was based on variance estimates from prior studies using GCSI-DD and the appetite VAS in patients with gastroparesis [41, 47], and was computed using a 2-

sided type I error rate of 0.05. Conservatively using the largest variance reported for any of the GSCI subscales, and conservatively using a within-subject correlation of 0.6, a sample size of 10 patients will provide 88% power to detect a 1-point decrease in GCSI-DD, which we judged to be a clinically meaningful change in the subscales and total scale. For a more likely within-subject correlation of 0.8, power would be >99%. For the appetite VAS, we judged a 10 mm change to be clinically significant. Again conservatively using the largest of the reported variances, 10 patients will give 80% power to detect a 10mm change if the within-subject correlation is 0.6 and 97% power if the within-subject correlation is 0.8. A sample size of 10 subjects will also provide sufficient precision in parameter estimates from this study for use in power calculations for future studies of olanzapine in patients with gastroparesis.

11 REGULATORY REQUIREMENTS

11.1 Informed Consent [1]

Informed consent will be signed in person by the subject after the protocol is explained by either the PI, co-I or study coordinator. If a subject is a patient of the PI or Co-I, the study coordinator will be responsible for obtaining informed consent to avoid potential issues of coercion. Before signing, subjects will be given ample opportunity to ask questions about the protocol. Consent forms will be signed in the Taubman Center or in the GI Physiology Laboratory in the Medical Procedures Unit. Please see Informed Consent for full details.

11.2 Subject Confidentiality

All study team members will make every effort to protect each subject's confidentiality. Participants will have privacy in a closed exam room to be able to provide information to the PI and/or study coordinator regarding medical history, current condition, and any other relevant information pertaining to the study. Research records, data, and/or specimens will be kept in a locked office and/or locked cabinet with access restricted only to study team members. Study members will also secure electronic data on computers by using password protection, installing and regularly updating security software, as well as encryption of data. Only the PI and the Study Coordinator will have

[1] The IRB may waive some or all elements of informed consent – consult the IRB for consenting requirements.

access to the data and subject identifiers. Only the PI and the Study Coordinator will be allowed to enter data onto the password-protected web-based server.

11.3 Unanticipated Problems[2]

All adverse clinical experiences, whether observed by the investigator or reported by the subject, must be recorded, with details about the duration and intensity of each episode, any actions taken, and the subject's outcome. The Principal Investigator must evaluate each adverse experience for its relationship to the study and for its seriousness.

The Principal Investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the Principal Investigator must provide details about the action taken and about the subject's outcome. The PI and study team will meet on at least a monthly basis to assess study recruitment, data integrity and quality, AEs, withdrawals, and compliance with the protocol plan. A DSMB will not be employed as this is a single-center open-label trial.

All AEs will be assessed by the Investigator(s) and will be recorded in the CRF, including the date of onset and resolution, severity, relationship to study medication, outcome, and action taken with study medication. All AEs will be reported to the IRB that meet reporting criteria. Toxicity will be graded according to the Common Toxicity Criteria as follows:
0 = No adverse event or within normal limits
1 = Mild AE, not requiring treatment

[2] The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (in the guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

An incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in order to protect the safety, welfare, or rights of subjects or others.

2 = Moderate AE, resolved with treatment
3 = Severe AE, resulted in inability to carry on normal activities and required professional medical attention
4 = Life threatening or disabling AE
5 = Fatal AE

Serious adverse event (SAE) is defined by the FDA as an AE resulting in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Once an AE or SAE is known, research team members at the study site will ensure that participants receive appropriate care and all actions taken by the PI and/or co-investigator after observing the AE or SAE will be documented.

The Principal Investigator is responsible for complying with local and institutional requirements related to the reporting and documenting of SAEs. These reports must include submission of all qualifying SAEs to the Institutional Review Board (IRB) and/or Independent Ethics Committee (or others). Any serious and unexpected AEs will be reported to the IRB and the FDA within 7 days of the occurrence or immediately if the event is fatal or life threatening. The guidelines established in the Committees on Human Research “Adverse Event and Unanticipated Problems Reporting Policy” will be followed.

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