Mount Sinai	Protocol Title:	Olanzapine for the treatment of Post-Discharge Nausea and Vomiting after Ambulatory Surgery
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	Date Revised:	1/31/2018
	Study Number:	GCO#15-1297; HSM# 15-00501

MSSM Protocol Template HRP-503a

Instructions:

1. *Prepare a document with the following sections. Note that, depending on the nature of your research, certain sections below may not be applicable. Indicate N/A as appropriate, explaining where possible.*
2. *For any items described in the sponsor's protocol, grant application or other source documents submitted with the application, you may reference the title and page numbers of these documents rather than cutting and pasting into this document.* ***Do NOT refer to any derived documents, such as the Sample Consent document, or other internal documents required with the submission.***
3. *If you reference page numbers, attach those pages to this protocol.*
4. *When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.*

Brief Summary of Research (250-400 words):

Ambulatory surgery is occurring with rapidly increasing frequency as surgical and anesthetic techniques have improved and pressure to reduce health-care costs has increased. While there are many benefits to recovering from surgery within the home, a significant disadvantage is the lack of rapid access to a healthcare provider when postoperative complications occur. Postoperative nausea and vomiting (PONV) are common after surgery and anesthesia, and recent studies have demonstrated a high incidence of post-discharge nausea and vomiting (PDNV) after ambulatory surgery, particularly in high-risk groups (female gender, age less than 50 years, history of PONV, opioid administration in the post-anesthesia care unit (PACU), and nausea in the PACU). Current practices known to reduce the risk of postoperative nausea and vomiting in the PACU, such as the avoidance of volatile anesthetics and the use of intraoperative ondansetron and steroids, have little effect on the risk of delayed PDNV. Novel strategies to prevent PDNV are needed. Orally administered olanzapine, which has been shown to decrease the incidence of chemotherapy-induced nausea and vomiting, demonstrates promise as a novel strategy for preventing PDNV. It has a long half-life, allowing for a single dose to be administered preoperatively. This study will evaluate whether there is a difference in the incidence and severity of PDNV between patients who receive oral olanzapine versus placebo prior to general anesthesia for ambulatory surgery.

1) Objectives:

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Research Question: Does the addition of olanzapine administered prior to anesthetic induction reduce the risk of PDNV within the first 24 hours after ambulatory surgery relative to placebo?

Primary Objective: Compare the rate of post-discharge nausea or retching/vomiting in patients who receive olanzapine versus placebo.

Secondary Objectives:

a) Measure the rate of post-discharge retching/vomiting in patients who receive olanzapine versus placebo.
b) Measure the rate of post-discharge nausea in patients who receive olanzapine versus placebo.
c) Measure the severity of post-discharge nausea in patients who receive olanzapine versus placebo using an 11-point Likert scale.

2) Background

Postoperative nausea and vomiting (PONV) are common complications that cause significant patient distress and dissatisfaction. PONV can increase costs, delay postanesthesia care unit discharge, and result in unanticipated hospital admission. In rare cases, serious medical complications can result, including postoperative bleeding, esophageal rupture, and pneumothoraces.[1] The incidence of postoperative nausea is approximately 50% and the incidence of vomiting is 30%.[2] As a result of its frequent occurrence and associated complications, PONV is a commonly evaluated quality and safety indicator.[3] The independent risk factors for PONV include female gender, history of PONV, non-smoking status, use of inhalational anesthetics, longer duration of anesthetic, use of postoperative opioids, and younger age.[4]

Ambulatory surgical procedures, which tend to be shorter in duration, are fortunately associated with less PONV in the recovery room. Recent studies however, have highlighted the magnitude of delayed post-discharge nausea and vomiting (PDNV). A large prospective multi-center study found a 37% incidence of PDNV after general anesthesia.[1] Given the rapidly increasing number of ambulatory surgical procedures performed, this amounts to 4.3 million patients with PDNV each year in the United States. Interestingly, only 20.7% of these patients suffered from PONV in the PACU prior to discharge. Most patients do not alert a healthcare provider when they suffer from nausea or vomiting after discharge, causing this frequent complication to remain under-

recognized.[5] PDNV can be significantly distressing to patients who are at home and no longer have access to intravenous antiemetic medication. Furthermore, patients who suffer from PDNV do not return to their normal daily activities until the nausea and vomiting have resolved.[5]

Independent predictors of PDNV include female gender, age less than 50 years, history of PONV, opioid administration in the PACU, and nausea in the PACU. A risk score for PDNV is based on these five factors.[1] Zero, one, two, three, four, and five of these factors are associated with a 7%, 20%, 28%, 53%, 60%, and 89% incidence of PDNV. Intraoperatively administered ondansetron, which has a half-life of approximately three hours, does not reduce the risk of PDNV. There is a trend toward decreased PDNV with intraoperative use of glucocorticoids, but the difference does not reach statistical significance. Avoidance of volatile anesthetics in favor of a total intravenous anesthetic technique (TIVA), which reduces PONV, does not affect the incidence of PDNV.[6] Given the high incidence of PDNV and paucity of effective prevention strategies, novel approaches for preventing this common complication are needed.

Olanzapine, an atypical antipsychotic medication in the thienobenzodiazepine class, antagonizes several receptors implicated in the pathogeneses of nausea and vomiting and has promising potential for the prevention of PDNV. Specifically, olanzapine antagonizes dopamine (D_1, D_2, D_4), serotonin ($5HT_{2A}$, $5HT_{2C}$, $5HT_3$), alpha-1 adrenergic, histamine (H_1), and multiple muscarinic receptors.[7] There is strong evidence for the antiemetic efficacy of olanzapine for both the prevention and treatment of chemotherapy induced nausea and vomiting (CINV).[8] A phase I study showed a maximum tolerated dose of 5mg during the two days prior to chemotherapy and 10mg for the next 7 days. Two phase II studies demonstrated efficacy with a similar protocol.[9,10]

Three randomized controlled phase III trials including 488 patients in total showed significant improvements in CINV prevention with antiemetic regimens that included olanzapine 10mg daily during treatment. Additionally, three randomized trials including a total of 323 patients showed efficacy for breakthrough CINV treatment with 10mg of olanzapine. Importantly, olanzapine was safe and well-tolerated in all trials without significant differences in adverse effects (including dizziness, sedation, and extrapyramidal symptoms) between treatment and control groups, although the majority of the studies were not double-blind. Long-term use of olanzapine is associated with weight gain, dyslipidemia, and increased risk of developing diabetes mellitus but these complications were not seen with short-term use for CINV prevention or treatment.[8]

To date, there is one small study examining the efficacy of olanzapine on the prevention

of post-operative nausea and vomiting. The results are promising in that 57% of patients in the placebo group required rescue antiemetic medications in the first 24 hours after surgery, whereas 37% of patients who received 10mg of oral olanzapine required breakthrough medication. This study included 82 patients undergoing general anesthesia for breast surgery who were randomized to receive placebo, olanzapine 5mg, olanzapine 10mg, or ondansetron 16mg prior to surgery. Outcomes measured were emetic episodes and need for rescue medications. Olanzapine and ondansetron showed similar efficacy in reducing nausea and vomiting. There was a trend toward increased efficacy of olanzapine 10mg compared to 5mg, but this did not reach statistical significance. There was no difference in frequency of adverse events between groups, including sedation, anxiety, restlessness, abnormal muscle movement, and headache.[11]

In the case of PDNV, the use of postoperative opioids is likely a significant contributory factor, as it occurs hours after the anesthetic agents have been metabolized. This is likely why the use of TIVA, which helps prevent PONV, has no effect on the incidence of PDNV. One mechanism of opioid-induced nausea and vomiting is mediated through D_2 receptors in the chemoreceptor trigger zone in the medulla oblongata.[12] This makes anti-dopaminergic agents, such as olanzapine, ideal to target opioid induced nausea and vomiting. The half-life elimination of orally administered olanzapine is 21-54 hours. The time to peak plasma concentration is approximately 6 hours. Therefore orally administered olanzapine, taken with a small sip of water prior to anesthetic induction, demonstrates ideal pharmacokinetics for the prevention of delayed PDNV. Olanzapine's long half-life, low cost, excellent safety profile with short-term use, and targeting of multiple receptors implicated in nausea and vomiting (especially $D_{2)}$ make it a hopeful prospect for the prevention of PDNV.

3) Setting of the Human Research

This study will be conducted at the Icahn School of Medicine at Mount Sinai. Consent will be obtained at the Mount Sinai OB/GYN Ambulatory Department at 1176 5th Avenue Klingenstein Pavilion E level clinic and OB/Gyn Mount Sinai Faculty Practice Associates (FPA) at 5 east 98th st

Study medications will be administered in the preoperative holding area in the sixth floor of the Annenberg Pavilion at 1468 Madison Avenue. The intraoperative protocol will take place in the operating room in which the case is scheduled. An investigator will evaluate the patient postoperatively in the Annenberg sixth floor PACU.

4) Resources Available to Conduct the Human Research

Prior to initiating this study, all participating investigators and support staff will conduct a protocol initiation meeting to ensure adequate knowledge of the study objectives, procedures, populations, and human subject protections. A log of meeting attendees will be maintained. The team of investigators includes anesthesiologists with expertise in anesthesia for ambulatory procedures, surgeons, and a biostatistician. A study physician will be available at all times for subjects to call regarding potential adverse effects related to the study drug.

The surgical co-investigators perform approximately 12 ambulatory surgical procedures requiring general anesthesia a week, and slightly less than half of those patients are less than 50 years old. By this estimation, there should be approximately 6 eligible patient per week, or 312 eligible patients in a year.

The Investigational Drug Service within the Mount Sinai Hospital Department of Pharmacy will be utilized to randomize consented patients to receive olanzapine versus placebo, and to supply the appropriate medication on the day of surgery.

5) Study Design

a) Recruitment Methods

Patients who consent to and are scheduled to undergo ambulatory surgery at Mount Sinai will be invited by their physician to participate in the study prior to the scheduled date of surgery at their routine preoperative visit at their physician's office. Office locations where recruitment will occur include: the Mount Sinai OB/GYN Ambulatory Department at 1[redacted], the OB/Gyn Mount Sinai Faculty Practice Associates (FPA) at [redacted] Upper East Side Gynecology at [redacted], Gramercy Gynecology at [redacted] t, New York Physicians at [redacted]. and the Plastic and Reconstructive Surgery Office at [redacted]. A flyer describing the study will be displayed at the first two clinic locations to advertise the study to potential participants. The flyer will instruct interested patients to discuss the study with their gynecologist, or to contact the principal investigator directly. If a patient tells their physician that they are willing to participate, a study investigator will describe the study in detail, answer questions, confirm participant understanding, and provide the written informed consent form for review. If the patient agrees, written informed consent will be obtained at this visit, with opportunity for the subject to withdraw at any time prior to the surgical procedure.

b) Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Adults age ≥ 18 and ≤ 50 years old
2. Patient scheduled to undergo ambulatory surgery under general anesthesia
3. Willing and able to provide informed consent

Exclusion Criteria:

1. Unable to swallow pills
2. Current use of typical or atypical anti-psychotic medications
3. History of allergy to olanzapine
4. Pregnancy/Lactation (subjects of child-bearing potential will have a urine pregnancy test performed the day of surgery)
5. History of QTcF > 450ms or torsades de pointes
6. Current use of antihypertensive medication
7. Diabetes Mellitus
8. Clinically significant cardiovascular disease defined as follows:
    a. Myocardial infarction or unstable angina within 6 months prior to the day of planned surgery.
    b. History of serious ventricular arrhythmia (i.e.: ventricular tachycardia or ventricular fibrillation) or cardiac arrhythmias requiring anti-arrhythmic medications, except for atrial fibrillation that is well controlled on anti-arrhythmic medication.
    c. New York Heart Association (NYHA) Class II or higher congestive heart failure.
9. Postural hypotension or vasovagal syncope within 6 months of planned surgery.

10. Hypotension on day of surgery, defined as a systolic blood pressure < 90mm Hg or a diastolic pressure < 60mm Hg.
11. Seizure disorder
12. Clinically active prolactinoma
13. Hepatic disease
14. Poorly controlled diabetes
15. Pre-operative blood glucose > 250 mg/dL
16. Narrow angle glaucoma
17. Parkinson's disease
18. Lewy body dementia

c) Number of Subjects

The majority of PONV interventions in use in current clinical practice reduce the risk by approximately 20%. This reduction is additive when multiple interventions are used. Assuming a 37% incidence of PDNV based on previous literature, to be powered to find a 20% reduction in risk from baseline the study must include 140 patients.

d) Study Timelines

Patients who consent to and are scheduled to undergo ambulatory surgery at Mount Sinai will be invited by their physician to participate in the study prior to the scheduled date of surgery at their routine preoperative visit. If a patient expresses interest in the study after viewing the recruitment flyer, arrangement will be made for an investigator to meet with the patient in clinic prior to the scheduled surgery to explain the study, screen the patient for eligibility, and obtain consent if appropriate. Patients who are consented will be randomized prior to their planned surgery. They will be followed for postoperative nausea and vomiting for 24 hours after discharge by telephone call on post-operative day one.

Based on the enrollment within the first year of the study, we expect to have 20-30 patients complete the study per year. Assuming that enrollment continues at the current pace, it will take approximately five years to enroll the necessary 140 patients. As patients only need to be followed for 24 hours after discharge to be assessed for all primary and secondary endpoints, we estimate the study will be complete within 2 weeks of final patient enrollment.

e) Study Endpoints

Primary Objective: Compare the rate of post-discharge retching/vomiting or nausea in patients who receive olanzapine versus placebo.

Secondary Objectives:

i) Measure the rate of post-discharge retching/vomiting in patients who receive olanzapine versus placebo.
ii) Measure the rate of post-discharge nausea in patients who receive olanzapine versus placebo.
iii) Measure the severity of post-discharge nausea in patients who receive olanzapine versus placebo using an 11-point Likert scale.

f) Procedures Involved in the Human Research

Subjects who consent to and are scheduled for ambulatory surgery under general anesthesia will be invited to participate in the study during a routine preoperative visit prior to the day of surgery by a study investigator. The details of the study will be reviewed and written informed consent will be obtained. Additionally, a flyer describing the study will be displayed at the two participating clinic locations to advertise the study to potential participants. The flyer will instruct interested patients to discuss the study with their gynecologist, or to contact the principal investigator directly. If a patient tells their physician that they are willing to participate, a study investigator will describe the study in detail, answer questions, confirm participant understanding, and provide the written informed consent form for review. Patients who have agreed to participate will have a 12-lead electrocardiogram (EKG) obtained in pre-surgical testing. Alternatively, if an EKG is not obtained prior to the day of surgery, it will be performed the same day in the assessment area prior

to surgery. Patient's with a QTc > 450 ms using the Fridericia formula will be excluded.

Subjects will be counseled verbally to avoid alcohol, benzodiazepines, and motor vehicle driving for 24 hours following discharge.

The name and date of surgery of the consenting patient will be given to the Investigational Drug Service of the Mount Sinai Pharmacy for randomization and preparation of the medication. On the day of surgery, an investigator will pick up the medication from the pharmacy for the individual subject, and have the subject take the medication with a small sip of water in the preoperative holding area within one hour prior to entering the operating room. In addition, the patient will be provided with a standardized diary to record episodes of vomiting for the first 24 hours after discharge and will be provided with verbal and written instructions for completing the diary (appendix 1). Subjects will be asked for a preferred contact number for the postoperative phone call and permission to leave a voicemail will be requested.

Upon entering the operating room, after application of standard monitors, midazolam 2 mg will be administered for anxiolysis. If endotracheal intubation is indicated, general anesthesia will be induced using fentanyl 3-5 mcg/kg and propofol 1.5-2.5 mg/kg and muscle relaxation achieved with succinylcholine 1-2 mg/kg or rocuronium 0.6 mg/kg, at the discretion of the attending anesthesiologist. Rocuronium will be administered as needed to maintain muscle relaxation during the case. If a laryngeal mask airway is to be used rather than an endotracheal tube, anesthesia will be induced with propofol 1.5-2.5 mg/kg. Regardless of method of airway management, anesthesia will be maintained with sevoflurane at concentrations deemed appropriate by the anesthesia provider based on intraoperative hemodynamic and respiratory monitoring. Additional doses fentanyl will be administered also as deemed appropriate by the anesthesia provider based on intraoperative hemodynamic and respiratory montitoring. All patients will receive dexamethasone 8 mg immediately following induction, and ondansetron 4 mg and ketorolac 30mg approximately 30 minutes prior to emergence from anesthesia unless there is a specific contraindication. Intubated patients will receive neuromuscular blockade reversal with neostigmine 0.4-0.7 mg/kg prior to tracheal extubation.

In the PACU, as needed ondanstron will be ordered as per the department standard orderset, (ondansetron 4 mg intravenous every 4 hours). However, the standard prochlorperazine 10 mg intravenous once will be removed from the orderset to reduce the risk of neuroleptic malignant syndrome or extrapyramidal symptoms when administered in combination with olanzapine. The patients' experience of nausea and/or vomiting will be assessed at 30, 60, and 120 minutes after surgery by trained study personnel. PACU EPIC records will also be audited to record the need for rescue antiemetic medications.

Prior to discharge from the PACU, subjects will be assessed for signs of orthostatic hypotension (a decrease of 20 mmHg in systolic blood pressure or 10 mmHg in diastolic blood pressure upon standing). Patients who meet the criteria for orthostatic hypotension will be evaluated and treated with intravenous fluid administration. Upon discharge, patients who had symptoms of orthostatic hypotension will be instructed to ambulate with assistance for the first 24 hours after discharge.

Information entered into the subjects' diary will be obtained during a telephone interview on the afternoon or evening of the first day following surgery. At this time investigators will also screen for adverse events.

Relevant preoperative, intraoperative, and postoperative data will be obtained from the anesthesia record, the EPIC electronic medical record, and the telephone interviews and collected on standardized forms by trained study personnel.

Data to be collected:

Age
BMI
ASA status
Smoking status
History of PONV
History of motion sickness
Total intraoperative fentanyl (mcg)
Total intraoperative propofol (mg)
Total intraoperative rocuronium (mg)
Total intraoperative neostigmine (mg)
Total intraoperative Sevoflurane
Duration of surgery
Total fentanyl dose in PACU (mcg)

Total oxycodone dose in PACU (mg)
Rescue antiemetics in PACU (yes/no) Ondansetron total dose (mg)
Length of PACU stay (minutes)
Vomiting in PACU (#episodes at least 1 min apart)
Nausea in PACU (highest number reported on 11 point Likert scale)
Post-discharge vomiting (#episodes at least 1 minute apart)
Post-discharge nausea (highest number reported on 11 point Likert scale)

g) Specimen Banking

N/A

h) Data Management and Confidentiality

All researchers who will access the data have completed the institutional HIPAA certification. Extracted data will be de-identified before being given to the statistician for analysis. Any intermediary data files containing extracted PHI will be stored on secured hospital servers and destroyed after data analysis is complete. All study data at Mount Sinai stored electronically will follow MSMC policies. All PHI that is not stored on a limited access Mount Sinai IT maintained network drive will be encrypted and password protected. Statistical analysis will be carried out by a statistician employed by the Department of Anesthesiology. When the de-identified data set are released for analysis, a one-way hash ID will be generated for each record. Only Mount Sinai study investigators with access to the full data set will be able to match the hash ID to the original source.

i) Provisions to Monitor the Data to Ensure the Safety of subjects

MSSM Principal Monitor (PI):
Last Name: Hyman
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MSSM Additional Monitor (Co-investigator):
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Dr. Hyman and Dr. Demaria are board certified anesthesiologists with expertise in the perioperative management of patients. All subjects will be called on post-operative day one by a study investigator. In addition to the routine post-operative day one phone call to the patient, all participants will receive instructions and a business card in order to have a point of contact to report a potential adverse event at any time during or after the study period. They will also be specifically informed that they should receive emergency department care for any signs and symptoms of hypotension. Patients who will not have anyone present at home after discharge will receive a same-day follow-up phone call from the study team to screen for adverse events.

The study remains blinded during the second year of enrollment and no interim analysis of efficacy has been performed. No adverse events have been reported by any study participants.

All adverse events will be recorded by the research team in a non-anonymized fashion and reported directly to the Mount Sinai Institutional Review Board.

The study team will report the following to the Institutional Review Board and FDA within 5 business days of when they became aware of the event:

Any event that, in the principal investigator's opinion, is unexpected and at least probably related to the study.

Any event that is expected but occurring with greater frequency/intensity will be reported to the Institutional Review Board and FDA within 5 business days.

The study team will report the following to the IRB and FDA on an annual basis:

All expected adverse events

The principal investigator will not enroll any new patients until the IRB has reviewed and responded to the report. The study team will continue to follow patients who are already enrolled.

Enrollment will continue once the IRB approves.

j) Withdrawal of Subjects

Patients may be withdrawn from the study without their consent if their eligibility changes from the time of initial consent to the start of surgery or, if in the opinion of the investigator, they are not appropriate for olanzapine administration.

6) Risks to Subjects

A single dose of 10 mg of olanzapine is expected to be safe with minimal risks to subjects based on multiple prior studies of olanzapine in chemotherapy-induced nausea and vomiting. The following risks of olanzapine have been described based on chronic use:

Likely (>10%)

Weight gain, dose dependent (5-40%)

Hypertriglyceridemia (≤39%)

Hypercholesterolemia (≤39%)

Somnolence, dose dependent (6-39%)

Extrapyramidal symptoms (EPS), dose dependent (15-32%)

Xerostomia (9-22%)

Weakness (2-20%)

Dizziness (4-18%)

Accidental injury (12%)

Insomnia (12%)

Elevated alanine aminotransferase (ALT) level (5-12%)

Constipation (9-11%)

Dyspepsia (7-11%)

Hyperprolactinemia (30%)

Hyperglycemia (12.8%)

Less Likely (1-10%)

Hypotension (2%)

Postural hypotension (1%)

Tremor (1%)

Asthenia (2%)

Akathisia reactions (2%)

Parkinsonism reactions (4%)

Rare but Serious (<1%)

Syncope

Sudden cardiac death

Hyperglycemia

Diabetic coma with ketoacidosis

Diabetic ketoacidosis

Acute hemorrhagic pancreatitis

Venous thromboembolism

Immune hypersensitivity reaction

Cerebrovascular disease

Seizure, status epilepticus

Suicidal intent

Pulmonary embolism

Death

Neuroleptic malignant syndrome (NMS)

Tardive dyskinesia

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Specifically, a trial comparing olanzapine versus aprepitant for prevention of CINV found no difference in scores between groups in a multi-symptom patient-reported outcome measure (MD Anderson Symptom Inventory (MDASI)), including drowsiness and fatigue.[13] A trial examining the effectiveness of olanzapine for treatment of breakthrough CINV similarly found no difference between groups in MDASI scores.[14] Another study comparing olanzapine with 5-hydroxytryptamine 3 (5-HT3) receptor antagonists for prevention of CINV found significant improvements in global health status, emotional functioning, social functioning, fatigue, nausea and vomiting, insomnia and appetite in the olanzapine group. There were no differences in weight, blood lipid or blood glucose levels between groups.[15] These trials support the safety and tolerability of short-term use of olanzapine.

Unlike the cancer patients receiving olanzapine for the prevention or treatment of CINV, patients in this study will be receiving general anesthesia and several other central nervous system depressing (CNS) medications, including intraoperative midazolam and fentanyl, and postoperative oxycodone. The combination of olanzapine and these medications may increase the risk of adverse events not see in the patients studied for CINV. These risks include sedation, respiratory depression, extrapyramidal symptoms, orthostatic hypotension and cardiac rhythm abnormalities

7) Provisions for Research Related Injury

Subjects will be monitored during surgery and during recovery from anesthesia. Upon discharge, subjects will be provided with a phone number to call should they have any concerns related to surgery, anesthesia, or the study. If necessary, subjects will be instructed to return to the hospital should any complication requiring medical attention occur.

Subjects who are injured as a result of this study will be treated until the resolution of the adverse event and the cost billed to them and/or their insurance carrier. Patients will not be compensated for research related injury.

8) Potential Benefits to Subjects

It is possible that patients who participate in this study and are randomized to receive olanzapine may be less likely to experience post-operative nausea or vomiting or that these symptoms may be less severe.

9) Provisions to Protect the Privacy Interests of Subjects

The de-identified data will be stored on secure, password-protected servers maintained by Mount Sinai Information Technology (IT). Access to the data will only be available to Mount Sinai IT administrators, the primary investigator, and co-investigators. When the de-identified data set are released for analysis, a one-way hash ID will be generated for each record. Only study investigators with access to the full data set will be able to match the hash ID to the original record. All investigators have completed HIPAA training regarding maintaining patient PHI confidentiality.

During preoperative evaluation, subjects will be asked what number they prefer to be contacted at after discharge. They will also be asked whether it is ok for an investigator to leave a message. All messages will be of a general nature and will not contain personal health information. Moreover, post-operative evaluation by phone on the day following surgery is routine practice.

10) Economic Impact on Subjects

There are no costs to subjects for participating in this study. Olanzapine or placebo will be provided to the subjects free of charge. There will be no additional visits or tests related to study participation.

11) Payment to Subjects

There is no payment to subjects

12) Consent Process

Eligible patients will be invited to participate in the study prior to the scheduled date of surgery at their preoperative visit. A study investigator will describe the study in detail, answer questions, confirm understanding, and provide the consent form for review. The voluntary nature of this study will be emphasized, and patients who initially agreed to participate may choose to decline participation on

the day of surgery. Participants will be asked about the study to confirm understanding prior to providing written informed consent. Only patients who speak English or Spanish will be enrolled. Spanish-speaking patients will be informed of the details of the study and have all questions answered by a co-investigator who is fluent in both Spanish and English, and will be provided the written consent form in Spanish. SOP HRP-090 will be followed.

13) Process to Document Consent in Writing

Consent will be documented using the standard PPHS consent template.

14) Vulnerable Populations

No vulnerable populations will be included in this study.

15) Multi-Site Human Research (Coordinating Center)

N/A

16) Community-Based Participatory Research

N/A

17) Sharing of Results with Subjects

Results will not be shared with individual subjects. Overall study findings describing the outcome of the study will be published in a peer-reviewed journal.

18) IRB Review History

This is a new IRB application

19) Control of Drugs, Biologics, or Devices

Note: The IDS has its own forms that must be completed and a review process that must be followed before the IDS representative will sign off on Appendix B for submission to the PPHS.

The Investigational Drug Service of the Mount Sinai Pharmacy will handle storage of the study medications. After consent is obtained, the subjects name, medical record, and date of surgery will be given to the research pharmacist for randomization. On the day of surgery, an investigator will obtain the medication from the pharmacy and bring it directly to the subject who will take it immediately under direct supervision of the investigator.

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