Effect of Bupropion on Seizure Threshold in Depressed Patients

Study Protocol and Statistical Analysis Plan

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1. **Protocol Title –** Effect of Bupropion on Seizure Threshold in Depressed Patients

2. Purpose of the study

Aim: Evaluate the effects of bupropion on seizure duration and seizure threshold during ultra brief right unilateral (RUL) electroconvulsive therapy (ECT). **Hypothesis:** Addition of Bupropion will increase seizure duration and lower seizure threshold.

3. Background and Significance

Depression is the leading cause of disability in individuals aged 15-44, resulting in 400 million disability days in a year (1). The total economic burden of the disease is estimated to be composed of $26.1 billion in direct medical costs, $5.4 billion in suicide-related mortality costs, and $51.5 billion in indirect workplace cost (1). Electroconvulsive therapy (ECT) is the gold-standard treatment for major depressive disorder (MDD) that is severe (2-5). The standard method of ECT used in the US now is right unilateral ultra-brief study. RUL ECT uses a pulse width of </= 0.3 ms, this optimizes electrical dosing and causes decreased severity of cognitive side effects. With right unilateral ECT it is essential for the stimulus to be above seizure threshold. The stimulus dosing is titrated to establish what seizure threshold is and this is titrated over the course of ECT sessions (6). Because the maximum ECT output is limited by FDA, a frequent problem encountered by ECT clinicians is high seizure threshold which at times cannot be provided by the ECT device and this compromises efficacy (7). Hence it would be useful to develop means to lower seizure threshold.

In addition, some studies show a reduction in efficacy with ultra-brief as compared to brief ECT with the former requiring higher number of ECTs to achieve remission in depression symptoms (8). There represents a need for increasing the efficacy for RUL ultra brief ECT given its favorable cognitive-side effect profile. Combining RUL ultra brief ECT with appropriate psychopharmacological agents to alter seizure profile is a feasible way of optimizing the efficacy.

4. Design and Procedures

4.1 Study protocol overview

The study is designed to evaluate the effect of bupropion on seizure threshold in patients with major depressive disorder (MDD) referred for RUL ultra brief ECT. The study is powered to determine changes in seizure duration and seizure threshold by enrolling 10 subjects. We plan to screen 20 subjects to have 10 participants.

The participant is not responsible for any research-related costs. The participants will be under the purview of their physician who is responsible for the participant's care. The study team will ask for participants' permission to contact ECT team so that information can be provided to the ECT team regarding the participant's enrollment during the study.

4.2 Screening

Potential participants will be discussed with the ECT team to which the patient would have been referred. Once a potential participant has been identified, a study team person will discuss the study and desire for participation in person with that individual during the ECT consult session which is needed prior to scheduling of the ECT session. If participants are found to be eligible they will be invited to participate in the study and

the study will be initiated in conjunction with their first ECT session. Participants will go through the informed consent procedure. After providing informed consent participants will undergo a clinical assessment to confirm the inclusion/exclusion criteria.

All female subjects in the reproductive age group will be tested for pregnancy using a commercially available test kit specified by Department of Obstetrics and Gynecology. The Pregnancy test must be negative to continue in the study. If sexually active, subjects must agree to use appropriate contraceptive measures for the duration of the study for inclusion. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use and will result in exclusion from the study.

4.3 Bupropion administration

Patients will receive ECT treatment as usual, however, study participants will be randomized to receive a single, extended-release bupropion (Wellbutrin® XL) 300 mg tablet to be taken by mouth, in the morning (4 hours prior to ECT) on the day of ECT session 1 or session 2. This will be a one-time administration of bupropion at this dose with no discontinuation of medications that patient is already on. There will also be no washout period before bupropion administration or ECT.

The study is powered to determine changes in seizure duration and seizure threshold by enrolling 10 subjects (5 subjects will receive bupropion prior to ECT session 1 and 5 will receive it prior to ECT session 2). Counterbalanced randomization will be used to assign subject drug administration to ECT session 1 or 2 with inter-individual cross-over. The PI (Steven T Szabo Jr MD PhD) and coordinator (Gopalkumar Rakesh) will be blinded to randomization details. Computer generated randomization would be done by Richard Weiner MD PhD – the director of the ECT program. The sleep lab clinical care coordinator (Mark Mayo) would be backup to generate randomization if Dr Weiner is absent.

The medication would be dispensed from Central Pharmacy in Duke North. It would be stored in the sleep lab in the red zone on the fifth floor of Duke South and carried by sleep lab clinical care coordinator (Mark Mayo) to the ECT suite for administration to study patients.

4.4 ECT administration

The clinical procedure of ultra brief RUL ECT in these subjects will not be deviated from the usual procedure that is described below. ECT treatments will be provided three times a week, with standard right unilateral electrode placement with a MECTA spectrum device (MECTA Corporation, Portland, Ore.) with a pulse width </= 0.3 and a current of 0.8 A. A standard dose titration procedure to determine seizure threshold will be conducted at the first and second treatments, subjects would receive bupropion during one of these sessions. Subsequent treatments would be administered at 5.5 times seizure threshold from the treatment session without bupropion administration.

4.5 Clinical assessments

The Montgomery-Asberg Depression Rating Scale (MADRS) is an assessment tool for depression symptom severity and will be carried out at baseline at every ECT visit. This is usual practice that the ECT clinician employs prior to the clinical administration of ECT. We will also measure time to orientation recovery post

ECT after the first and second ECT treatments.

4.6 Blood collection

During ECT sessions 1 and 2, just prior to administration of right unilateral (RUL) ECT, patients will be placed with a venous catheter and we will acquire a 3 mL blood sample to be used to ascertain serum bupropion level.

4.7 Timeline of Assessments

Assessments	ECT Session 1	ECT Session 2
Screening	X	X
RUL ECT seizure profile	X	X
MADRS Rating Score	X	X

5. Subject Selection - Inclusion and exclusion criteria

Inclusion Criteria

(1) Male and female subjects, age >25 years.
(2) Meeting diagnostic criteria for major depressive disorder per DSM5.
(3) Referred for ultra brief RUL ECT.
(4) Right motor dominant.
(5) Competent to provide informed consent.
(6) Able to read or comprehend English.
(7) H/O treatment with bupropion. Subjects need to be off bupropion for at least a week to be included.
(8) Concomitant treatment with benzodiazepines, dosing of which has remained stable for a week prior to study ECT session.

Exclusion Criteria

(1) Lifetime history of schizophrenia, bipolar disorder, schizoaffective disorder, mental retardation, seizure disorder.
(2) Current alcohol abuse or dependence within past 6 months.
(3) Current substance abuse or dependence within past 6 months.
(4) Recently received ECT within preceding 3-6 months.
(5) Currently on any formulation of bupropion.
(6) Currently on any anticonvulsants or clozapine.
(7) Pregnancy test positive
(8) Contraindications to use of bupropion, which include the following:
- Eating disorder
- MOAI use in the past 14 days
- Levodopa or amantadine use
- Abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs
- Known hypersensitivity to bupropion or other components of study drug

(9) BUN > 20 mg/dl or serum creatinine >1.5 or AST> 41 U/L or ALT > 63 U/L or total bilirubin >1.5 mg/dl

6. Subject recruitment and compensation

We will recruit both inpatients and outpatients referred for ECT. Patients are referred by private physicians and by clinical services within Duke University Health Systems and other psychiatric facilities. Inpatients admitted on Williams' Ward in Duke South (4th floor red zone) will be approached for participation after discussion with the ECT team they have been referred to. Outpatients will be recruited in the manner as described in section 4.2. Selection criteria for subjects has been described in Section 5. Capacity to consent will be assessed by a member of the treatment team who is not an investigator on this study (such as the inpatient attending psychiatrist or the unit director). Study team members (who are not members of the subject's clinical team) will approach potential subjects after the study is introduced to potential subjects first by the ECT Team attending. For both inpatients/outpatients referred to ECT recruitment would proceed as follows: 1) study team member reviews charts for ECT consult roster to ID potential eligible individuals 2) Discuss with ECT team whether someone is appropriate 3) A member of patient's clinical ECT team asks patient if they want to hear about study and 4) With patient agreement, study team member discusses study with them. Study team member discussing informed consent will fully disclose and explain the risks and benefits of the study procedures, and answer the patient's questions about the study and the material presented in the informed consent form. Alternatives to study participation will be discussed, and the voluntary nature of participation in the study will be emphasized. This consent discussion will be documented in a consent note placed in the patient's chart.

There would be no compensation for patients in this study. We do not deviate from usual course of treatment except for a one-time administration of bupropion which is an antidepressant and an additional session of seizure threshold titration. Subjects would receive standard of care and there are no additional visits or rating scales applied as part of the study.

7. Consent Process – see Section 14 of the e-IRB submission form

8. Subject's Capacity to Give Legally Effective Consent – All patients recruited for this study must have capacity to give legally effective consent.

9. Study Interventions – This has been described in detail in section 4.3

10. Risk/benefit assessment

The potential risks of the study design are problems associated with ECT and administration of extended-release bupropion administration and possible suicidal ideation. Risk and benefits are for procedures done specifically for the study.

10.1 Potential risks

10.1.1 ECT

Immediately following ECT, patients are typically disoriented or confused. Following ECT sessions, some patients report headache, muscle soreness, or nausea. These side effects usually respond to simple treatment. Serious medical complications are rare. Cardiac complications are more common and constitute the leading cause of morbidity and mortality with ECT. The likelihood of these complications is reduced by (1) careful medical workup and the use of cardiology consultants in patients with significant preexisting cardiac disease; (2) careful monitoring of cardiac status during ECT; (3) modification of anesthetic procedures for prophylactic purposes (e.g., use of pharmacological agents to block hemodynamic changes). Fatality associated with ECT is estimated to occur in 1/10,000 patients, and to our knowledge has never occurred at Duke.

ECT commonly results in memory deficits. These memory deficits are of two types: anterograde and retrograde amnesia. There is little objective evidence that memory impairments persist more than four weeks following an ECT course. The effect of ECT on memory is cumulative, depending on number of sessions. It is unusual to see these deficits after the first or second treatments.

The magnitude of both memory deficits depends on parameters used in the conduct of ECT. In general, these deficits are more severe with bilateral (BT) versus right unilateral (RUL) electrode placement. Spacing of treatments may be increased or the treatment course terminated in the context of unacceptable side effects.
For the study, patients would have seizure threshold estimated during second ECT in addition to seizure threshold estimation during the first. This exposes them to debatable cardiovascular risk from sub convulsive stimulations (9). Some rare but concerning adverse effects related to supra-threshold stimulus titration of ECT in elderly patients are post-ECT delirium/confusion and persistent memory impairment (6)

10.1.2 Specific risks/side effects of bupropion

Like all antidepressants, bupropion increases the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term trials. These trials did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in subjects aged 65 and older. Other common side effects are tachycardia, insomnia, headache, agitation, dizziness, constipation, weight loss and nausea. Patients with a history of a seizure disorder or head trauma with loss of consciousness could have a seizure with bupropion.

10.1.3 Risk of spontaneous seizure with simultaneous administration of bupropion and ECT

Seizure risk is 0.1 % for 450 mg of sustained release Bupropion. This risk is comparable to that of other antidepressants (10).

Regarding safety for combined use of Bupropion and ECT, we found 3 case reports that reported the occurrence of seizures when this combination was used together. In 2 case reports there were other medications used in addition to bupropion, and one case report had discontinuation of benzodiazepine such as clonazepam contributing to seizure occurrence (11-13). In all these patient scenarios, they received bilateral (BT) ECT, and the bupropion administered was immediate release (IR) and not sustained release (SA). Another set of 3 case reports do talk about the safe administration of the combination of bupropion with ECT with no occurrence of spontaneous seizures other than those that occurred as part of ECT(14, 15).

10.1.4 Risk of spontaneous seizures with ECT

There are case reports and studies that detail the development of spontaneous seizures after a course of ECTs or after a few ECTs (16-18). The incidence of the phenomenon is less than 0.1%. We plan to use only 300 mg sustained release bupropion. The SA preparation offers a steady level of bupropion, thus minimizing risk of seizures.

10.1.5 Evaluation procedures
The medical evaluations present no risks beyond what is expected for routine clinical care of a patient undergoing a course of ECT.

10.1.6 Risks of blood collection
As described above, blood collection will occur twice (3 ml each time) through a catheter placed in the individual's arm vein just before they receive ECT. Complications of drawing blood from a catheter which is placed in an individual's arm vein for a brief period occur at approximately 2% of the time, and include discomfort at the site of puncture, possible bruising and swelling around the puncture site, and rarely infection or faintness from the procedure.

10.2 Methods to minimize risks: - The following are methods to minimize risks associated with this study

10.2.1 Screening of participants prior to study enrollment
As described above, the screening assessment of potential participants will identify and exclude from participation individuals with current or past medical conditions that may place them at increased risk for adverse effects from ECT. Screening will include assessment of medical history, neurological history (seizure, stroke, and brain lesion), head trauma, pregnancy, and substance abuse/dependence. Screening will be performed by physician evaluation, physical examination, and blood work.

10.2.2 Supervision of participants during ECT sessions
ECT sessions will be conducted by the study investigators and physicians. These personnel will be in visual and auditory contact with the patients always. Health status will be monitored continuously as described in the protocol.

10.2.3 ECT device safety features
The ECT device has internal limits on stimulation parameters. These limits prevent the device from being programmed to deliver pulses that exceed predetermined limits. The device logs all parameter values.

10.2.4 Minimizing risks associated with blood collection
To minimize the risks of drawing blood from a catheter vein, sterile techniques will be used by trained individuals.

10.2.5 Minimizing risk of seizures with bupropion
We will use the sustained release formulation of bupropion. Review of literature indicates 300 mg of sustained release formulation to be a safe dose in patients (10). The sustained release preparation reaches peak level more gradually compared to other preparations of bupropion.

10.3 Risk and benefit analysis
As outlined above, extensive precautions will be taken to ensure of the safety of study participants. All patients participating in this study will receive treatment with a full course of electroconvulsive therapy as part of their routine clinical care. The study is proof of concept and would provide data

to design a larger trial aimed to optimize psychopharmacology in conjunction with RUL ultra brief ECT to lower seizure threshold.
Estimation of seizure thresholds will be done twice in this study, which exposes subjects to debatable cardiovascular risk due to sub convulsive stimulations. However, for the study, it is imperative that we measure differences in seizure threshold between the first and second ECT sessions to estimate the differences in seizure threshold caused by bupropion administration. The study will inform us about the effect of bupropion on seizure parameters in patients with major depressive disorder. This would help us optimize ECT treatments for patients with depression.

Costs to the Subject – Subjects would not incur any costs because of participation in this research study. There would be no compensation for patients in this study. We do not deviate from usual course of treatment except for a one-time administration of bupropion which is an antidepressant and an additional session of seizure threshold titration. Subjects would receive standard of care and there are no additional visits or rating scales applied as part of the study. **The study sponsor would pay for the study drug and blood draws to obtain bupropion serum levels.**

11. **Data Analysis & Statistical Considerations** We will use mixed effects modeling to see if extended-release bupropion influences seizure parameters in ECT. The independent grouping variable will be session (ECT session 1 vs ECT session 2) with primary outcome variables being seizure duration and seizure threshold. There are no previous studies that have looked at effect of bupropion on seizure threshold apart from case reports and hence it becomes difficult to calculate an ideal sample size to get good study power. We plan to recruit only 10 patients as this would be a pilot study.

12. **Data & Safety Monitoring**

Data and safety monitoring will follow standard protocol procedures. Any serious adverse event will be reported within 24 hours to the Duke IRB. Adverse events will be documented and addressed accordingly. The participants will be fully informed of the nature of the study requirements prior to enrollment and periodically throughout the study. The participants' well-being will be continuously monitored by the experimenter, and the Principal Investigator will report all serious adverse events in an expedited manner to the Duke University Health System (DUHS) Institutional Review Board (IRB) office and all applicable regulatory authorities in accordance with the Center's standard operating procedures. The study monitor will be Dr. Steven Szabo. Dr. Szabo will ensure the quality of the study and establish that all study staff are complying with the investigational plan and IRB regulations. Monitoring of this protocol is simplified by the fact that this study involves a small number of investigators and a single facility in which the study is being conducted. Throughout the investigation, the monitor will ensure that the facilities being used continue to be acceptable for the purposes of the study, that the investigational plan is being followed, that any changes to the protocol have received IRB approval and have been reported to the sponsor, that accurate, complete, and current records are maintained, that accurate, complete, and timely reports are made to the IRB. This will be accomplished through quarterly meetings during which the status of the protocol, investigators, and IRB compliance are reviewed. The monitor will review each research chart for completeness and accuracy. He will confirm that inclusion and exclusion criteria have been met for each subject enrolled, and compliance with all other aspects of the investigational plan are met.

13. Privacy, Data Storage & Confidentiality – see Section 12 of the e-IRB submission form and complete the questions in that section

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