Burst Suppression Anesthesia for Treatment of Severe Depression

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Brief Title: Anesthesia for Treatment of Depression

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Supported by:

Department of Psychiatry
University Neuropsychiatric Institute
Department of Anesthesiology
University of Utah

Table of Contents

1. Schedule of Activities

Visits	Screening	Baseline	1	2	3	4	5	6	7	8	9	10	Post Tx	Follow-up[5] (Repeated)
Assessments			**Week 1**				**Week 2**			**Week 3**				
Inclusion/Exclusion	X	X												
Consent		X												
Psychiatric Interview		X												
HRSD, MoCA, WSAS, GAD7		X						X					X	
MRI / MRS		X						X					X	
QIDS			X	X	X	X	X	X	X	X	X	X		
Randomization[1]		X												
Standard Monitoring			X	X	X	X	X	X	X	X	X	X		
EEG			X	X	X	X	X	X	X	X	X	X		
Blood Sample			X									X		
Anesthetic Induction[2]			X	X	X	X	X	X	X	X	X	X		
Anesthetic Emergence[3]			X	X	X	X	X	X	X	X	X	X		
QIDS, WSAS, Study XP[4]														X

[1] Study 1 only

[2] High ISO/BS+, Low ISO/BS-, or propofol

[3] Time to eye opening, time to sitting without dizziness, and time to ambulation and ingestion of liquids without vomiting. Occurrence rates of nausea and vomiting, presence of EKG abnormalities and somatic complaints, and total time for each will also be recorded. Orientation time will be assessed as the earliest time post-treatment at which a participant is able to recall 4 of 5 orientation items (name, date of birth, age, place, day of the week).

[4] An opened ended question about the participant's experience during the study

[5] Follow-up measures will take place monthly after the end of treatment series and will continue for 6 months.

2. Study Objectives

2.1 Study 1

Study 1 will test the central hypothesis that high dose isoflurane anesthesia inducing EEG burst suppression (High ISO/BS+) is a more effective intervention for severe depression when compared to a low dose isoflurane anesthesia that does not induce EEG burst suppression (Low ISO/BS-). The proposed study is a randomized, double-blind trial that will evaluate 30 actively depressed participants with moderate to severe depression. Depression outcomes will be compared between two groups of participants (n=15 per group) who have received 10 treatment applications over a period of three weeks of either High ISO/BS+ or Low ISO/BS-.

Aim 1. To determine whether High ISO/BS+ is more effective than Low ISO/BS- in producing either a treatment response (defined as 50% reduction in depression scores) or full remission of depressive symptoms. We hypothesize that significantly more depressed participants randomized to receive 10 treatments of High ISO/BS+ compared to Low ISO/BS- will show a positive treatment response or full remission by treatment end. Based on the STAR*D Trial, a responder is a participant showing 50% reduction in depression score and full remission is defined as a score of 0-10 on the HRSD-24 scale and score of 0-5 on the QIDS-SR_{16}.

Aim 2. Preliminary data on neural and immune pathways that are differentially affected by the 2 treatments and associated with antidepressant effects will be explored by comparing changes from pre-treatment to post-treatment in full transcriptome leukocyte gene expression (using the RNA Seq method).

Aim 3. To measure the central neurochemical effects of isoflurane treatment, we will quantify neurotransmitter levels (GABA and glutamate) using magnetic resonance spectroscopy.

2.2 Pilot Study 2

Study 2 is designed to complement Study 1 in providing additional support for the hypothesis that burst suppression is an important mechanism for antidepressant treatment effects of anesthesia in moderate to severe depression. If Study 1 demonstrates that more participants receiving High ISO/BS+ undergo remission than those receiving Low ISO/BS-, this could be interpreted as a dose response effect for isoflurane that is not specifically a result of burst suppression. Demonstrating that a different anesthetic administered at doses producing 80% burst suppression for 10 treatment session is also effective in producing depression remission would add support for the hypothesis that the underlying mechanism is burst suppression. Therefore, Study 2 will be an open-label trial to provide preliminary data that propofol, an intravenous anesthetic with a favorable safety profile, administered for 10 treatment sessions at levels to induce 80% burst suppression, also is effective in producing depression remission in 50% or more of the pilot sample of 10 depressed participants.

Aim 4**.** To determine whether propofol anesthesia at a level to produce 80% EEG burst suppression is effective in producing remission of depressive symptoms. We hypothesize that

the majority of depressed participants (n=10) receiving 10 treatments of propofol anesthesia will achieve remission of symptoms by treatment end.

Aim 5**.** Preliminary data on neural and immune pathways that are differentially affected by the 2 treatments and associated with antidepressant effects will be explored using full transcriptome leukocyte gene expression (RNA Seq).

Aim 6. To measure the central neurochemical effects of propofol treatment, we will quantify neurotransmitter levels (GABA and glutamate) using magnetic resonance spectroscopy.

3. Background

Major Depressive Disorder is a prevalent, chronic, recurring disorder that is becoming increasingly burdensome both to individuals and society at large. Despite the increasing burden of this disease, we have seen a plateau in development and establishment of effective treatments, particularly for those who are refractory to conventional medications. Electroconvulsive therapy (ECT) is typically regarded as the treatment of choice for the most treatment resistant depression (TRD) as it rapidly reduces symptoms and yields high remission rates (about 55-90%) even after multiple medication failures. [8, 9, 17, 18, 20] Though effective, ECT is associated with significant adverse cognitive effects such as retrograde amnesia, problems with concentration and attention, and other cognitive sequelae. [6, 15] There is also a widespread public misunderstanding that the seizure induced by ECT may be painful, and carries risk of brain damage and personality change. These fears make patients and family members reluctant to approve this treatment option. [15, 16] For these reasons, this effective therapy is often used a treatment of last resort (relegated to 5th, 6th or 7th step after the failure of other therapies per American Psychiatric Association guidelines) and ECT is administered to only about 100,000 of the millions of TRD patients each year. For TRD patients, there is a great need for alternative therapies with similar efficacy to ECT but wider social acceptability and less adverse cognitive effects.

One such treatment alternative that may be both efficacious and have a better side effect profile is deep inhalation anesthesia with isoflurane. Like ECT, deep anesthesia with isoflurane induces a brief state of electrocortical quiescence (flat electroencephalogram), but does not induce convulsions or other seizure symptoms. Anesthesia-induced cortical burst suppression was first suggested as a potential alternative to ECT for treatment resistant depression in the 1980's. Recent research, both clinical and preclinical, has renewed interest in this hypothesis.

Langer et al [11, 12] originally hypothesized that high dose isoflurane anesthesia (High ISO) might be an effective antidepressant therapy based on certain similarities to the physiological effects of ECT. The feature shared by High ISO and ECT was a reduction in electrocortical activity, which occurs after the seizure in ECT and without any seizure in High ISO anesthesia. In their study of ECT treatments, Kranaster et al [10] noted that post-ictal burst suppression index correlated with seizure duration, and thus was predictive of antidepressant effectiveness. The hypothesis that cortical burst suppression (BS+) is important in anesthesia-induced antidepressant effects has

not been rigorously studied in patients, but has been reinforced by recent findings using animal models of depression including research by our co-investigators. [19, 21] Murrell et al [14] had previously reported that at equivalent anesthetic concentrations, isoflurane had greater potency to induce BS+ than 2 related anesthetic drugs, sevoflurane and desflurane, and that another inhaled anesthetic, halothane, did not induce burst suppression (BS-). Using the forced swim test, Tadler et al [19] found that High ISO anesthesia had antidepressant effects in mice similar to the antidepressant desipramine. Similarly, using a shuttle box-based test of learned helplessness in rats, Wang et al [21] found that 2 hours of isoflurane at 2% prevented this depressive behavior while halothane-treated rats (who experienced no EEG burst suppression) showed no preventive antidepressant effects. Whether cortical burst suppression is the mechanism for the antidepressant effect of isoflurane anesthesia in patients and animal models remains an important and unresolved research question.

Initial trials examining the antidepressant efficacy of High ISO were promising. Langer et al [11, 12] conducted two preliminary studies that demonstrated comparable efficacy between 6 sessions of High ISO vs. ECT, with High ISO having the advantage of not causing memory loss. Antidepressant efficacy was also supported by Engelhardt et al [3] who used High ISO treatments followed by ECT and by Carl et al [1] who again found comparable antidepressant efficacy with the 2 treatments. These positive findings were followed by two negative trials. Greenberg et al [5] treated 6 elderly individuals with High ISO, with little improvement. Garcia-Toro et al [4] examined the efficacy of 4 low dose treatments of a related anesthetic, sevoflurane, in another pilot trial, and saw a 24% reduction in depressive symptoms. Since sevoflurane is less effective in inducing BS+ than isoflurane, the dose could have been too low to achieve consistent BS+. Moreover, 4 treatments are fewer than are recommended for ECT (8-12 sessions) and thus it is not surprising that the effect size was small. Unfortunately, further investigations of High ISO as an antidepressant halted for quite some time.

Because of its early success and the design limitations associated with the negative trials, our group conducted a small open-label study to renew investigation of the potential antidepressant efficacy of High ISO. [22] In the study, 8 patients with treatment resistant depression were treated with 10 sessions of high dose ISO with confirmed EEG burst suppression (High ISO/BS+). The comparison group was 20 patients treated with bifrontal ECT. High ISO/BS+ led to an antidepressant response (defined as a 50% reduction in HRSD score) in 75% of participants and a rate of full remission of depressive symptoms identical to ECT (50%). Furthermore, the response rates for the High ISO/BS+ and ECT treatments were comparable, as measured by QIDS self-report. In addition, improvement was maintained for 4 weeks after treatment for most participants in the High ISO/BS+ group. Furthermore, participants treated with High ISO/BS+ showed significantly less neurocognitive impairment following their treatments than was shown by ECT-treated patients.

The central question in the proposed research is whether isoflurane-induced cortical burst suppression (BS+) is necessary for antidepressant efficacy in patients with severe depression. We demonstrated that BS+ (defined as ≥80% burst suppression ratio (BSR) using the Bispectral Index BIS Monitor) can be reliably induced at high isoflurane concentrations that are clinically

safe in our target population while on various psychotropic medications. [22] However, to date, there has been no rigorous randomized, blinded trial comparing antidepressant effects of High ISO/BS+ to an appropriate control condition. The present study is designed to provide this rigorous test using a control condition involving a lower isoflurane dose that predictably produces unconsciousness in this same patient population without causing burst suppression (BS-, defined as ≤20% BSR). Thus, we will determine if high dose ISO anesthesia inducing EEG burst suppression (High ISO/BS+) is a more effective intervention for severe depression when compared to a low dose ISO that does not induce EEG burst suppression (Low ISO/BS-).

As an additional test of whether cortical burst suppression is a possible mechanism underlying anti-depressive effects of deep anesthesia, we will also examine the antidepressant effects of burst suppression induced by propofol, an intravenous anesthetic with a favorable safety profile that is routinely used by anesthesiologists. This closely associated study will be an open-label trial to provide preliminary data that may support the use of propofol for this group of depressed patients. Propofol is the agent of choice to induce burst-suppression for brain protection during neurosurgical procedures and is used routinely for this purpose. Propofol does not promote post treatment nausea; however, like isoflurane, propofol is associated with dose dependent hypotension. This is well tolerated by patients without cardiovascular disease and is easily treated as described for isoflurane. Although anecdotal data support some anti-depressant effects with propofol, these effects have not been specifically or systematically examined. If effective, its use may be an even better option than isoflurane for patients, for the reasons described above.

If evidence from these studies support deep anesthesia with BS+ (High ISO/BS+ and/or propofol/BS+), it would point to a possible mechanism of action for the antidepressive effects of deep anesthesia. Treatments that evoke burst suppression, in theory, could have all the benefits of ECT without the neurocognitive deficits and the associated social stigma.

As detailed above, even in the minority of cases when initial pharmacological treatment for depression is effective, it usually requires months before symptoms show satisfactory remission, and during that time patients and physicians have no objective test to use to verify that the intervention is or is not likely to be successful. Even with ECT, where improvement can be noted in days rather than weeks or months, initial signs of improvement are based on relatively soft non-objective measures such as global improvement that rely heavily on the physician's individual clinical insight and experience. Thus, there is a great need to establish convenient, reliable and objective biomarkers for treatment-induced changes that reliably predict clinical improvement in cases of depression.

By comparing changes in full transcriptome leukocyte gene expression from pre- to post-treatment in these 40 participants treated with High ISO/BS+ vs. Low ISO/BS-, and propofol/BS+, this investigation will explore the neural and immune pathways through which anesthetic-induced antidepressant effects are produced, and will be able to identify candidate neural pathways that can later be reconfirmed in larger samples. In particular, we will examine the possible role of NMDA receptor subunits, GABA-ergic and ATP-responsive ion channel

pathways as well as other putative depression- or suicidality-linked neuroimmune pathways previously associated with refractory depression or suicidality by our group and others. [2 7 13]

Burst suppression anesthesia is thought to strongly engage the brain's major inhibitory and excitatory neurotransmitter systems, GABA and glutamate, respectively. Indeed, both isoflurane and propofol are thought to directly bind GABA and glutamate receptors. To better understand the brain mechanisms through which burst suppression causes antidepressant effects, we will measure GABA and glutamate concentrations in vivo using magnetic resonance spectroscopy, a type of MRI.

4. General Study Design

To determine if the antidepressant effects of deep anesthesia are related to burst suppression (BS+) we will conduct two concurrent studies: 1) prospective, randomized, double-blind study will evaluate the role of burst suppression using isoflurane treatments at 2 doses (high dose ISO/BS+ vs low dose ISO/BS-) on symptoms in participants with moderate to severe depression, and 2) an open-label pilot study examining the anti-depressive effects of propofol anesthesia, BS+ same as high dose ISO/BS+ on symptoms in participants with moderate to severe depression.

4.1 Inclusion Criteria

We will recruit depressed patients referred to the University Neuropsychiatric Institute for an ECT consult.

- Diagnosis of Major Depressive Disorder (MDD) or bipolar Disorder (I or II, most recent episode must be depression
- Failed at least 2 anti-depressant treatments and no ECT in past 6 months
- Age between 18-55 years
- BMI < 40
- Hamilton Rating Scale for Depression (HSRD) score > 18
- Quick Inventory of Depression Scale (QIDS) score > 10.

4.2 Exclusion Criteria

- Diagnosis of other current and/or active DSM-5 disorders with the exception of anxiety disorders
- Significant pre-morbid cognitive impairment
- Hypertension and current use of ACE inhibitor or AR blocker medications
- Symptomatic coronary artery disease or congestive heart failure
- History of transient ischemic or neurologic signs during the past year
- History of or susceptibility to malignant hyperthermia
- Contraindication to isoflurane or propofol anesthesia (as determined by anesthesiologist)
- Diabetes requiring insulin
- Poor kidney function
- Chronic use of benzodiazepines or opioids

- Individuals incompetent to provide consent (e.g. catatonic, psychotic).

4.3 Study Recruitment Procedures

Potential participants will be recruited to the study through one of three ways: chart review, referral, or direct enrollment.

Recruitment via chart review: Potential participants will first be identified through review of medical records by trained study staff; specifically, examination of the records of patients who have been scheduled for an ECT consultation at the University Neuropsychological Institute (UNI). Participants who may be eligible for screening will be told about the study toward the end of their consultation. Interested patients will be screened and consented either right after the ECT consultation or during a separate appointment.

Recruitment via referral: Physicians from the Department of Psychiatry who have been informed of this study may also refer patients for screening. Patients who are referred will be contacted by study staff to arrange for screening and consent.

Direct enrollment: Psychiatrists listed on the study protocol may identify potential research volunteers during their ECT consultations. These patients will be informed of the research, and if interested, will be screened and consented.

Participants will be informed that there are two study options and that they will be able to decide which one they will participate in. For the isoflurane study, we will explain that some preliminary evidence shows that high dose isoflurane is effective in reducing depression symptoms. However, if the isoflurane study is chosen, there is a 50:50 chance of being in the low dose isoflurane treatment, and the individual will not know what treatment group (high vs low dose) they are in. We do not know whether low dose isoflurane will reduce depression symptoms. For the propofol study, we will explain that this arm of the study is open-label, meaning they will know they are receiving propofol treatment at a dose that produces burst suppression. We will also inform participants that we do not know if propofol treatment will be effective in reducing symptoms of depression.

We hope to enroll at least 1 participant per week and have a maximum capacity of 4 participants per week with a total of 45 participants enrolled in the study (30 in Study 1 and 10 in Study 2).

4.4 Informed Consent Procedures

Trained research staff will screen potential participants and obtain consent. Participants will be consented in the physician's office (if consent is after the ECT consult); otherwise, consent will take place in a private meeting room near the ECT Clinic at UNI. No other language than English will be used to obtain consent.

Participants and study coordinator (and/or physician) will go over each section of the consent form together. They will then be given time to read/ think about/ discuss/ and ask questions

about the study before they sign. Thus, they may sign at that time, or we may schedule another visit to sign and enroll into the study. Most of these patients have a support person with them who will be included in the consent process (provided the participant is fine with it). A legally authorized representative (LAR) will NOT be used to consent the participant.

We will make certain the participant understands that the experimental treatments may or may not be effective. We are not offering any financial inducement for participation. Participants are not required to sign the consent right after we explain it. If necessary, we will schedule a later date for consent to allow adequate time for participants to ask questions and think about whether to participate in the study.

Psychiatrist Investigators on this protocol may consent patients if they see an eligible patient in a context other than an ECT consult. We don't anticipate that many participants will be enrolled via this route.

4.5 Study Visits

Screening: Patients who have been referred or have volunteered for the study will be screened in person or by phone to verify that inclusion and exclusion criteria have been met.

Consent procedures: Each patient will be given a full verbal explanation of the study procedures, including risks, benefits, and alternatives, and will be given a copy of the approved written consent form. The patients will be given the opportunity to review the consent form and to discuss any questions or concerns with their own psychiatrist, our study investigators, or others if necessary prior to beginning study treatment procedures.

Baseline: Prior to the first treatment, depression severity will be assessed via a psychiatric interview, including completion of the HRSD-24 and MoCA, which will also verify inclusion and exclusion criteria. Immediately before treatment 1, the participant will complete the QIDS and a blood sample will be obtained from the IV line.

Randomization (Study 1 only): Participants who meet study criteria will be randomly assigned in blocks of 4 to either high or low dose isoflurane (High ISO/BS+ vs. Low ISO/BS-). We anticipate up to 15 participants in each arm; this sample size was defined by our prior study in which 8 participants were adequate to show significant antidepressant effects.

Leukocyte Gene Expression: Although our study is designed with EEG burst suppression as our primary target mechanism, we acknowledge that its effects must be mediated via specific neural pathways. Thus, we will explore possible neural and immune pathways associated with the antidepressant effects of deep anesthesia. Changes in full transcriptome leukocyte gene expression from pre- to post-treatment will be assessed from blood samples drawn before the first treatment and within 48 hours of the final (10^{th}) treatment. In particular, we will examine the possible role of GABA-ergic and ATP-responsive ion channel pathways as well as other putative depression- or suicidality-linked neuroimmune pathways. We will also evaluate other ATP-responsive ion channels (purinergic, acid sensing and transient vanilloid receptor) or other

genes including IL-10 and other cytokines, SAT1, PTEN, MARCKS and MAP3K3 previously associated with refractory depression or suicidality by our group and others. [42918]

Magnetic resonance imaging: GABA and glutamate concentrations will be quantified in the prefrontal cortex and a posterior cortical control region using 2-dimensional J-resolved proton magnetic resonance spectroscopy (MRS) and prior knowledge fitting (Prescot & Renshaw, 2013) on the Siemens Prisma 3T scanner at the Imaging & Neurosciences Center in Research Park. In case that scanner is unavailable, images will be acquired using an identical scanner at the University Neuropsychiatric Institute. Time in the scanner is expected to be 60-75 minutes (maximum: 90 minutes). The scans will be completed prior to beginning the treatments, before treatment #6, and 48-72 hours post treatment #10.

Costs and Compensation

There are no costs to participate. No compensation will be provided to participants.

Subject Withdrawal and Study Completion

Subject compliance will be monitored throughout the trial by study staff. If any contraindications to the study are identified, participants may be withdrawn by the investigators. Participants can be withdrawn at any point if the investigators feel it is in the participant's best interest or in the interest of study integrity. No information will be collected from withdrawn participants unless it is related to a continuing AE or SAE.

5. Clinical and Laboratory Evaluations

5.1 Study Drug Administration and Duration

All treatment groups, High ISO/BS+, Low ISO/BS- (Study 1) and propofol (Study 2) will receive 10 treatments over 3 weeks. All treatment procedures will take place in the ECT Procedure Room at the University of Utah Neuropsychiatric Institute. All participants will receive standard monitoring as recommended by the American Society of Anesthesiologists that includes EKG, pulse oximetry, blood pressure by noninvasive cuff, temperature, respiratory rate, and end-tidal carbon dioxide. If monitoring reveals significant hemodynamic alteration the anesthesiologist will manage the study participant by one or more of the following: IV fluid loading; Trendelenburg positioning; small bolus doses of ephedrine, phenylephrine, or epinephrine; or stopping the anesthesia. The course of action will be at the discretion of the anesthesiologist based on initial hemodynamics, absolute MAP change, and condition of the study participant. IV fluids will also be co-loaded at induction with the goal of replacing any deficit that resulted from fasting. The above noted anesthetic practices are routine and carried out on a daily basis in both the operating room and in the ECT suite.

5.1.1 Study 1. High vs Low Dose Isoflurane (ISO): The route and doses of isoflurane (both high and low doses) fall within the normal range of standard clinical practice. Details of induction follow, below:

Anesthetic Induction (High and Low Dose ISO): Anesthetic induction will be achieved with methohexital (1-3mg/kg IV). If there is a contraindication to methohexital, etomidate or propofol will be administered at the discretion of the anesthesiologist. General anesthesia will be administered via facemask. Patients will be co-loaded with IVF to offset any dehydration from fasting. Patients will be ventilated while under anesthesia using an LMA or ET tube as appropriate for safety and comfort.

High ISO/BS+ (n=15): The High ISO/BS+ group will receive isoflurane at the same level used in our previous study, with the initial vaporizer setting at 4%. End-tidal isoflurane concentration will measured continually and is the best measure of alveolar concentration. Alveolar concentration will approximate effect site concentration. In this study we are directly measuring isoflurane effect on CNS electrical activity via the EEG (BIS) and burst suppression ratio is continually calculated and displayed. As the end tidal isoflurane concentration increases and the burst-suppression ratio increases, the vaporizer setting will be decreased. The goal is a burst-suppression ratio of 80%. Some burst suppression is seen at concentrations as low as 1MAC of isoflurane (1.15%) and most patients will achieve 80% BSR at 2 MAC or less (2.3%). These doses are well within the normal range for isoflurane use and are achieved on a daily basis in the O.R.s at this institution. As in the prior study by Weeks et al [51], this condition of isoflurane-induced electrical quiescence will be maintained for 15 minutes.

Low ISO/BS- (n=15): ISO concentration will be titrated to maintain unconsciousness with burst suppression of ≤20%. This condition will be maintained for 15 minutes.

5.1.2 Study 2. Open-Label Propofol Treatment: Participants in the propofol treatment group will receive an induction dose of 2-3 mg/kg IV bolus, followed by propofol infusion at 100-400 mcg/kg/min. Additional boluses (0.5-2 mg/kg), administered every 2-3 minutes, may be necessary to achieve and maintain 80% burst suppression on EEG. At the end of the treatment, propofol administration will be discontinued and the participant will be allowed to awaken. Similar means of propofol induced burst-suppression is commonly and safely administered during neurosurgical procedures. Monitoring and supportive treatment will be consistent with clinical standards outlined by the American Society of Anesthesiologists as discussed above for participants in the main study. We will enroll up to 10 participants in the propofol pilot study.

5.1.3 Anesthetic Emergence (All Treatments): Emergence from isoflurane anesthesia into consciousness will be facilitated by the Aneclear device (QED 100^{TM}) according to FDA approved guidelines and as routinely used in the University of Utah operating rooms.

The time from discontinuing the intervention to when the participant responds to the repeated (every minute) command “Open your eyes” will be recorded. Participants will be monitored for AEs such as nausea, vomiting, and sore throat during anesthetic emergence. Orientation will be assessed repeatedly, beginning 3 minutes after eye opening, until the participant answers the questions correctly, e.g. “What day is it”, “Do you know where you are?” Perception of drug

effects during recovery will be assessed using the Drug Effects Questionnaire (DEQ). The total time for each session (estimated at 1.5 to 2.5 hours) will also be recorded.

5.2 Study Drug Management

Study drug will be managed by staff at the University Neuropsychiatric Institute. Subjects will be issued a subject ID number. This number will be used to randomize subjects into High ISO/BS+ or Low ISO/BS- arms of the study. Randomization will be conducted by a designated un-blinded member of the study team. Emergency un-blinding information will be maintained by a designated custodian. Subjects' un-blinding information will only be accessed by the study team in case of a medical emergency. If a drug disclosure is made, a record must be made by the Investigator detailing the purpose, date, and personnel involved.

5.3 Clinical Assessments

5.3.1 Primary Response Assessments: The primary outcome measure is change in depressive symptoms assessed by the Hamilton Rating Scale for Depression (HRSD-24), which is the most widely used method of evaluating the effectiveness of treatments to relieve depression. HRSD-24 will be administered as part of a clinical interview by blinded investigators prior to beginning the treatments, then repeated before treatment #6 and at the end of treatments.

5.3.2 Secondary Response Assessments to be acquired before each treatment: Also as standard of care for patients receiving ECT, the participant will fill out the Quick Inventory of Depressive Symptomatology (QIDS-SR) which is a patient self-report measure of depressive symptoms prior to each treatment session. QIDS scores will also be used as a safety measure. If 2 consecutive QIDS scores indicate worsening of depressive symptoms, below pre-treatment values, the study participant will meet with one of the study Psychiatrists to discuss treatment alternatives. The Montreal Cognitive Assessment (MoCA), Generalized Anxiety Disorder scale (GAD-7), and Work and Social Adjustment Scale (WSAS) will be administered prior to beginning the treatments, then repeated before treatment #6, and 48-72 hours post treatment #10.

5.3.3 Follow-up Assessments to be acquired monthly for up to 6-months post treatment period: Follow-up assessments will include QIDS-SR, WSAS, and an opened ended question about the participant's experience during the study. Follow-up assessments will be administered over the phone or by email with a link to an electronic survey housed on REDCap (a secure online database). A voicemail may be left (with prior permission) regarding the follow-up assessments.

5.4 Tissue Banking

Blood samples will be drawn from participants and analyzed for biomarkers of depression and response to treatment. Samples will be stored in a -80 freezer in Dr. Mickey's laboratory at 383 Colorow or in Dr. Alan Light's laboratory in the Department of Anesthesiology, U of U School of Medicine.

Participants who consent to bank de-identified samples will be assigned a study code that is linked to their identifying information during the study period. After all study blood analyses are performed, the study coordinator will determine which samples (by code) need to be de-identified. When these samples are located, they will be assigned a new code that is not linked to personal identifiers. This de-identification process will happen after all study blood analyses are completed.

Participants who want their samples to be removed from the bank must contact Dr. Mickey. If their samples are still linked to identifying information, they will be located and destroyed. De-identified samples will not be removed, as it will not be possible to identify their source.

De-identified banked samples will be available to researchers within the University of Utah and at the institutions of research collaborators. All researchers must contact Dr. Mickey to receive permission to conduct IRB approved research on depression and response to treatment using these samples.

6. Data and Safety Monitoring

We will monitor study data and documentation after the first 2 participants have completed treatment and then every 6 months thereafter. The monitoring group will consist of Ken Johnson, MD, MS, Professor of Anesthesiology; Shane Brogan, MD, Associate Professor (Clinical) of Anesthesiology; and Jim Ashworth, MD, Associate Professor (Clinical) of Psychiatry. This group is well qualified to review data and safety reports for the study.

6.1 Data Collection

Discussion of the study with participants will take place individually instead of in front of a group. The data collected through research interventions will be conducted in a private place. The information collected about participants will be limited to the amount necessary to achieve the aims of the research so that no unneeded information will be collected. Gene expression data gathered during this study will not be shared with the participant or family members.

6.2 Data Storage

Research data will be stored on password protected computers or in locked cabinets or offices. All participant identifiers will be stored separately from the coded, participant data.

Any data that will be transferred or transported outside of the institution will be encrypted. Any research information shared with outside universities or entities will be de-identified.

Periodic review and confirmation of participant eligibility and informed consent documentation will take place. This review will also include confirmation that all appropriate information has been reported to the oversight agencies (IRB).

6.3 Safety and Efficacy Monitoring

All serious adverse events will be reported within 5 days to the Data and Safety Monitoring Board (DSMB) and IRB by the Principal Investigator or study coordinators. These would include life-threatening cardiac arrhythmias, respiratory arrest, myocardial infarction, stroke, and death. Moderate adverse events including worsening of depressive symptoms will be reported to the DSMB. An interim data analysis will be performed at the midpoint of this pilot investigation, after data is obtained from 5 participants in each of the treatment conditions. The study will be terminated if significantly greater negative outcomes are associated with either isoflurane treatment or propofol treatment.

Prior to each treatment, participants will fill out the QIDS-SR. HRSD-24 will be obtained at baseline, before treatment 6, and after treatment 10. All participants will be assessed before the 6th treatment. If participants in Low ISO/BS- or propofol treatment groups show clinical deterioration (defined by 2 consecutive QIDS scores below baseline OR a decrease in HSRD-24 before the 6th treatment), they will be offered treatment at the 80% burst suppression level (High ISO/BS+) as it has proven effective in reducing depression or ECT as the standard of care treatment. Participants in High ISO/BS+ treatment who show clinical deterioration, as defined above, will be offered ECT. All serious adverse events will be reported within 5 days to the DSMB by the Principal Investigator or study coordinators. The DSMB will also be notified within 10 business days if a study participant is showing signs of clinical deterioration (defined as 2 consecutive QIDS scores below baseline OR HRSD-24 below baseline). Progress reports will be submitted every 6 months. If a participant has a serious reaction to anesthesia, they will be withdrawn from the study.

As exploratory biomarkers, we will evaluate whether quantitative cortical EEG changes early in treatment (obtained from dual lead BIS data in each treatment session) are associated with subsequent remission in depressive symptoms.

7. Statistical Considerations

Statistical analyses will employ a statistical mediation model framework. Any participant missing necessary information will be excluded from statistical analysis. Only participants with usable data will be included in the analyses. If the original statistical plan becomes infeasible, the original plan and the modifications made will be reported.

7.1 Aim 1. To determine if significantly more depressed participants randomized to receive 10 treatments of High ISO/BS+ will show a positive treatment response (defined as 50% reduction in depression scores) or achieve full remission of symptoms by treatment end compared to those in the Low ISO/BS-group, odds of treatment response and remission will be compared between groups using logistic regression analysis with positive response at treatment end (yes/no) as the dependent variable, and treatment group (High ISO/BS+ vs Low ISO/BS-) as the independent variable. Positive treatment response is defined as 50% reduction in depression scores, and remission will be defined as a score of 0-10 on the HRSD-24 scale.

Covariates will include baseline depression severity and possibly other baseline demographic and clinical measures as needed.

7.2 Aims 2 and 5. Using RNA SEQ methods, we will also explore whether participants who respond to treatment show blood-based changes in gene expression of neural and immune pathways previously associated with refractory depression or suicidality by our group or others. A t-test or non-parametric Wilcoxon test will be used, as appropriate. Change from baseline to end of treatment in gene expression levels will be correlated with change from baseline to end of treatment in HRSD-24.

7.3 Aim 4. In the open-label trial of propofol, initial evidence of efficacy will be defined by the percent of participants who show at least a 20% reduction in both HRSD and QIDS scores (initial improvement, as employed in the STAR D investigation) and who are propofol/BS+ responders (defined as 50% or more reduction in both HRSD-24 and QIDS scores). Secondary evidence of efficacy will be defined by comparing the percent of participants who are responders to propofol/BS+ vs. to the Low ISO/BS- control condition in the randomized trial.

8. Training and Resources

Brian Mickey MD, PhD, Principal Investigator, is trained in Psychiatry and is an established researcher in the area of neuroscience and treatment-resistant depression. He will oversee the project.

All anesthetic treatments will be administered by experienced Anesthesiologists from the Department of Anesthesiology (Drs. Tadler, Smith, Sakata, Odell, Jessop, Larson, Whittingham, and Beck). Drs. Tadler and Smith will coordinate the anesthesiology team.

Psychiatric evaluations (HSRD-24 interviews) will be performed by experienced psychiatrists from the Department of Psychiatry (Drs. Weeks, Mickey, Kendrick, Gilley, Pierson, and Bushnell).

Kathleen Light, PhD, Department of Anesthesiology, has over 30 years of NIH-funded research and will assist the PI with data analysis, publications, and preparation of a larger grant proposal using data from this project.

Alan Light, PhD, Department of Anesthesiology, will supervise the gene expression assays for the biomarker portion of the study.

Andrea White, PhD, Department of Psychiatry, will be responsible for coordinating patient screening and scheduling participant visits. She will oversee collection and initial processing of blood samples for the biomarker portion of the study. She will be responsible for randomization, maintaining the subject coding key, and monitoring study progress.

Anna Arp, study coordinator, Department of Psychiatry, will assist with participant recruitment, screening, and management of study records.

Core members of the study team will meet regularly (typically weekly) to discuss study progress, including recruitment, data management, and participant status.

All study personnel have current CITI training. Personnel who are responsible for data monitoring and study reports will have had appropriate RATS training. All personnel who will consent study participants have experience with this process and have received specific guidance regarding the details of this protocol.

All treatments will take place in the ECT suite at the University Neuropsychiatric Institute. Screening, consent, and psychiatric interviews will take place in office space adjacent to the ECT suite.

Participants will undergo psychiatric evaluation at baseline, after treatment #5, and after treatment #10. In addition, before each treatment, depression will be assessed using the QIDS. If a participant is in need of immediate psychiatric care, the UNI CrisisLine is available 24/7.

9. Protection of Human Subjects

9.1 Potential Risks

Isoflurane is a standard anesthesia induction agent. Its use has been shown to be effective in standard surgical care. Isoflurane is contraindicated if: 1) the participant is sensitive to isoflurane or other halogenated anesthetics, or 2) if the participant or a family member have had previous complications from anesthesia, specifically malignant hyperthermia.

Propofol is a well-tolerated, routinely administered anesthetic. Its use has been shown to be effective in standard surgical care. Propofol is contraindicated if the participant has an allergy to soy or peanuts.

The following risks are associated with anesthesia:

Common (1-10%): The participant may experience nausea, vomiting, and/or shivering from the anesthesia. Medications can be given to help with nausea and vomiting. These symptoms normally resolve within 60 minutes. Participants may also experience a mild sore throat from the breathing tube. For propofol group only: burning sensation at the injection site.
After each anesthesia treatment, activities requiring mental alertness may be impaired for 2-4 hours. Therefore, we require participants to have someone accompany them home and recommend that they do not make any important decisions for 24 hours after treatment.

Both isoflurane and propofol anesthesia are associated with dose-dependent decreases in blood pressure. If monitoring reveals significant hemodynamic alteration, the anesthesiologist

will manage the study participant by one or more of the following: IV fluid loading; Trendelenburg positioning; small bolus doses of ephedrine, phenylephrine, or epinephrine; or stopping the anesthesia. The course of action will be at the discretion of the anesthesiologist based on initial hemodynamics, absolute MAP change, and condition of the study participant."IV fluids will also be co-loaded at induction with the goal of replacing any deficit that resulted from fasting. Blood pressure typically returns to normal after anesthesia is stopped.

Very Rare (less than 1/10,000): Complications including life-threatening cardiac arrhythmias, respiratory arrest, myocardial infarction, stroke, and even death are possible. These events are much less likely in adults who are younger than age 55 and who have low cardiovascular risk. Malignant hyperthermia is another very rare complication of isoflurane anesthesia. We are excluding participants who have a known susceptibility to this condition.

The physicians performing these procedures are experienced anesthesiologists and will be closely monitoring responses to the anesthesia and all vital functions, and will take all appropriate steps to minimize these risks.

Risks of Worsening Depression
During the psychiatric and HSRD-24 interviews, participants will be asked to answer questions about their symptoms that may be upsetting. The interviews will be conducted by experienced clinicians in Psychiatry who have expertise in managing emotional situations. If participants require additional support, they will be referred to their clinical provider or the UNI CrisisLine at (801) 587-3000.

The study physicians will be monitoring participants' depressive symptoms at frequent intervals, and if symptoms get worse, we will discuss other treatment options available outside of the study. Treatments available after leaving the study may include ECT or medications.

Risks of Blood Sampling
Blood samples will typically be obtained through the participant's IV line, but we may have to do an additional needle stick in some cases. Thus, there is the risk of pain, bruising, and in rare cases infection. Sampling will be performed by skilled personnel to minimize these risks.

Risks of MRI
Standard questionnaires and screening procedures will be performed prior to MRI scanning to rule out MRI contraindications (e.g., pacemakers, surgical clips, metallic devices). Subjects and all investigators will be screened for metallic objects prior to entering the scanner room. Subjects will wear hearing protection to prevent hearing damage due to scanner noise.

REPRODUCTIVE RISKS
The effects of isoflurane and propofol on the embryo or fetus are currently unknown. It is possible that if either of these is given to a pregnant woman it will harm the unborn child. Pregnant women must not take part in this study, nor should women who plan to become

pregnant during the study. Women who are at risk of pregnancy will be asked to have a pregnancy test before taking part to exclude the possibility of pregnancy. If you could become pregnant you must use an effective contraceptive during the course of this study. Acceptable methods of birth control include abstinence, oral contraceptives, the contraceptive patch, the contraceptive ring, condoms, etc.

9.2 Potential Benefits

There may be no direct benefits to participants who volunteer for this research, although evidence suggests that participants receiving High ISO/BS+ may realize a clinical benefit. Information obtained from this work may provide insight into the role of burst suppression as a possible mechanism underlying the anti-depressant effects of deep anesthesia. The gene expression analyses may in turn identify potential neuro-immune pathways associated with depression treatment.

10. References

1. **Carl C, Engelhardt W, Teichmann G, Fuchs G.** Open comparative study with treatment-refractory depressed patients: electroconvulsive therapy--anesthetic therapy with isoflurane (preliminary report). Pharmacopsychiatry. 1988;21(6):432-3.
2. **Cattaneo A, Gennarelli M, Uher R, Breen G, Farmer A, Aitchison KJ, et al.** Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline 'predictors' and longitudinal 'targets'. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2013;38(3):377-85.
3. **Engelhardt W, Carl G, Hartung E.** Intra-individual open comparison of burst-suppression-isoflurane-anaesthesia versus electroconvulsive therapy in the treatment of severe depression. European journal of anaesthesiology. 1993;10(2):113-8.
4. **Garcia-Toro M, Segura C, Gonzalez A, Perello J, Valdivia J, Salazar R, et al.** Inefficacy of burst-suppression anesthesia in medication-resistant major depression: a controlled trial. The journal of ECT. 2001;17(4):284-8.
5. **Greenberg LB, Gage J, Vitkun S, Fink M.** Isoflurane Anesthesia Therapy: A Replacement for ECT in Depressive Disorders? Convulsive therapy. 1987;3(4):269-77.
6. **Group UER.** Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. Lancet. 2003;361(9360):799-808.
7. **Iacob E, Light KC, Tadler SC, Weeks HR, White AT, Hughen RW, et al.** Dysregulation of leukocyte gene expression in women with medication-refractory depression versus healthy non-depressed controls. BMC Psychiatry. 2013;13(1):273.
8. **Khalid N, Atkins M, Tredget J, Giles M, Champney-Smith K, Kirov G.** The effectiveness of electroconvulsive therapy in treatment-resistant depression: a naturalistic study. The journal of ECT. 2008;24(2):141-5.
9. **Kramer BA.** Use of ECT in California, 1977-1983. The American journal of psychiatry. 1985;142(10):1190-2.
10. **Kranaster L, Plum P, Hoyer C, Sartorius A, Ullrich H.** Burst suppression: a more valid marker of postictal central inhibition? The journal of ECT. 2013;29(1):25-8.
11. **Langer G, Karazman R, Neumark J, Saletu B, Schonbeck G, Grunberger J, et al.** Isoflurane narcotherapy in depressive patients refractory to conventional antidepressant drug treatment. A double-blind comparison with electroconvulsive treatment. Neuropsychobiology. 1995;31(4):182-94.
12. **Langer G, Neumark J, Koinig G, Graf M, Schonbeck G.** Rapid psychotherapeutic effects of anesthesia with isoflurane (ES narcotherapy) in treatment-refractory depressed patients. Neuropsychobiology. 1985;14(3):118-20.
13. **Le-Niculescu H, Levey DF, Ayalew M, Palmer L, Gavrin LM, Jain N, et al.** Discovery and validation of blood biomarkers for suicidality. Molecular psychiatry. 2013;18(12):1249-64.
14. **Murrell JC, Waters D, Johnson CB.** Comparative effects of halothane, isoflurane, sevoflurane and desflurane on the electroencephalogram of the rat. Laboratory Animals. 2008;42(2):161-70.
15. **Payne NA, Prudic J.** Electroconvulsive therapy: Part I. A perspective on the evolution and current practice of ECT. Journal of psychiatric practice. 2009;15(5):346-68.
16. **Payne NA, Prudic J.** Electroconvulsive therapy: Part II: a biopsychosocial perspective. Journal of psychiatric practice. 2009;15(5):369-90.

17. **Prudic J, Olfson M, Marcus SC, Fuller RB, Sackeim HA.** Effectiveness of electroconvulsive therapy in community settings. Biological psychiatry. 2004;55(3):301-12.
18. **Shiwach RS, Reid WH, Carmody TJ.** An analysis of reported deaths following electroconvulsive therapy in Texas, 1993-1998. Psychiatric services. 2001;52(8):1095-7.
19. **Tadler SC, Light,A.R., Hughen R.** Isoflurane demonstrates antidepressant-like activity in a mouse model of depression. . Anesthesia and Analgesia. 2009;108:212.
20. **Tess AV, Smetana GW.** Medical evaluation of patients undergoing electroconvulsive therapy. The New England journal of medicine. 2009;360(14):1437-44.
21. **Wang L, Elmer,G.I., Mayo,C.L., Gould,T.D., Shepard,P.D.** Isoflurane impedes the development of a depression-like phenotype in rats. Society for Neuroscience Annual Meeting Planner. 2012;665.06/X17.
22. **Weeks HR, 3rd, Tadler SC, Smith KW, Iacob E, Saccoman M, White AT, et al.** Antidepressant and neurocognitive effects of isoflurane anesthesia versus electroconvulsive therapy in refractory depression. PLoS One. 2013;8(7):e69809.
23. Prescot AP & Renshaw PF. Two-Dimensional J-Resolved Proton MRSpectroscopy and Prior Knowledge Fitting (ProFit) in the Frontal and Parietal Lobes of Healthy Volunteers: Assessment of Metabolite Discrimination and General Reproducibility. J Magn Reson Imaging. 2013 Mar; 37(3): 642–651.