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Riluzole Augmentation Pilot in Depression (RAPID) Trial

I. Background and Significance

Affecting an estimated 151.2 million people worldwide, depression remains the leading cause of years lived in disability.[i] Unfortunately, first-line treatments for major depression, primarily agents that inhibit reuptake of monoamines (serotonin, dopamine, and nor epinephrine) achieve symptomatic remission in only one to two thirds of patients, depending on the number of medication trials.[ii] Standard antidepressant medications, primarily selective serotonin reuptake inhibitors (SSRIs) also take four to eight weeks to work, [iii] and with the majority of patients requiring multiple trials of medications, patients can remain symptomatic for several months. [iv] During this time, depressed individuals not only experience the disability associated with social withdrawal, low energy, decreased concentration, sleep problems, and appetite disturbance, but also potentially acute risks arising from suicidal thoughts and behaviors.[v] As a consequence, there is a great need for novel antidepressant agents that are more effective and rapidly acting.

Recent attention has focused on the glutamatergic system as a new, distinct target for depression treatment. [vi,vii] Dysregulation of glutamate, the primary excitatory neurotransmitter in the central nervous system, has been the primary excitatory neurotransmitter in the central nervous system, has been associated with depression in humans as well as animal models. [viii] These observations have been further heightened by preliminary clinical experience with ketamine, a glutamatergic NMDA receptor antagonist and AMPA receptor modulator with anesthetic properties.

In small placebo-controlled crossover studies, single-dose intravenous ketamine has demonstrated a significant antidepressant effect within hours among individuals with treatment-resistant major depression [ix] and bipolar depression. [x] While the response from ketamine can be striking, the effect typically wanes over the course of days. While the response from ketamine can be striking, the effect typically wanes over the course of days. For treatment-resistant patients, one open-label study with repeated, scheduled dosing was similarly effective and well tolerated for up to two weeks,[xi] though the longer-term safety and efficacy of ketamine treatment remains unknown. In addition, sedation, dissociation, and psychotic symptoms represent potential side effects. Nonetheless, in light of the dramatic results seen with ketamine, the relevance of glutamate neurotransmission in psychiatric illness continues to grow, with some authors arguing that "glutamate-based depression" represents a distinct, though common, phenotype of the disorder. [xii]

Riluzole (Rilutek, Sanofi), an oral modulator of glutamate activity with neuroprotective and anticonvulsant properties, is currently approved by the United States Food and Drug Administration for treatment of amyotrophic lateral sclerosis (ALS). In patients with ALS, riluzole has been shown to modestly slow progression of the disease and prolong time until death. [xiii] In vitro, riluzole has the capacity to reduce excess glutamate activity though several mechanisms, most uniquely by enhancing astrocytic glutamate uptake. [xiv] Importantly, while riluzole modulates glutamate transmission, it does not share the psychotomimetic or anesthetic effects of ketamine at physiologic concentrations. The net effect of riluzole on glutamate activity includes a relatively rapid increase in brain-derived neurotrophic factor (BDNF) expression and promotion of hippocampal neurogenesis [xv], one proposed final mechanism for antidepressant efficacy. [xvi]

Recent animal studies of riluzole have supported its antidepressant properties. In a rodent model of depression (chronic unpredictable stress), riluzole not only improved behavioral measures, but also reversed the stress-induced glial pathology typically seen in the prefrontal cortex. [xvii] In the olfactory bulbectomy model of depression, rats given riluzole showed significant, dose-dependent improvement in hyper emotionality scores after one administration as well as with repeated, sub-chronic dosing. [xviii] In chronic (22-day) administration of riluzole, rats showed improvements in immobility time during the forced swim test, indicative of a sustainable antidepressant effect. [xix]

Preliminary studies using riluzole to treat depression in humans are also promising, though larger, double-blinded controlled trials are needed. An open-label trial of riluzole in ten patients with severe treatment-resistant depression led to a 9.6-point (36%) reduction in Hamilton Depression Rating Scale (HDRS) score in six weeks. [xx] A similar 8-week trial augmenting lithium treatment in acutely depressed bipolar patients yielded a significant reduction in Montgomery-Asberg Depression Rating Scale (MADRS) scores, without eliciting any hypomania or mania. [xxii] Positive results with riluzole have also been seen in small open trials of patients with generalized anxiety disorder and obsessive-compulsive disorder, [xxiii] suggesting anxiolytic as well as antidepressant effects.

This proposed study sets out to examine the antidepressant effects of riluzole in two novel ways. The first is by using a double-blinded design, addressing the significant issue of placebo response seen in antidepressant trials. [xiv] To our knowledge, this methodology has not yet been used in any published riluzole trials among patients with unipolar depression. Second, unlike previous studies that have specifically examined patients with treatment-resistant depression, already subject to current and past medication trials, we propose using Riluzole alongside standard serotonin reuptake inhibitor therapy in currently untreated major depression. By doing so, we seek to examine the potential role of riluzole as a first-line augmentation agent, with the hypothesis that it will improve the

problematic efficacy and response time inherent in standard antidepressant therapy.

II. SPECIFIC AIMS

This study will determine if riluzole augmentation of standard sertraline monotherapy leads to a more rapid and complete antidepressant response among individuals with untreated major depressive disorder.

The specific objectives are:

1) To examine the additive effect of riluzole on absolute HDRS scores, remission rate, response rate, and time to antidepressant response

2) To evaluate the tolerability of initiating riluzole and standard SSRI therapy simultaneously in treatment-naïve individuals, and

3) To assess any beneficial changes in co-morbid anxiety symptoms as measured by the HARS.

It is hypothesized that compared to SSRI treatment alone, dual therapy with SSRIs and riluzole will be equally well tolerated and lead to a greater reduction in HDRS and HARS scores, greater response and remission rates as well as shorter time to response.

III. SUBJECT SELECTION

Overall study population:
Adult outpatients with a current, untreated major depressive episode.

Inclusion Criteria:
- Adults (ages 18-75) who meet DSM-IV criteria for a major depressive episode,
- Hamilton Depression Rating Scale (HDRS) >22, and
- No antidepressant treatment for at least three weeks.

Exclusion Criteria:
- Active drug or alcohol disorder in the past 3 months
- History of psychosis, history of mania or hypomania
- Epilepsy or history of seizures
- Hypothyroidism
- Congenital QTc prolongation
- Liver disease
- Lung disease
- Acute suicide or homicide risk
- Pregnant women, breastfeeding women, women of childbearing age not using

contraception
- Unstable medical illness
- Elevated thyroid-stimulating hormone (TSH>5.0mlU/L), or
- Abnormal liver function tests (ALT>50 U/L or AST>50 U/L)
- ADD / ADHD (Attention deficit hyperactivity disorder)

Disallowed therapies include: other psychotropic medications, including antipsychotics, mood stabilizers, benzodiazepines, barbiturates, other sedative-hypnotics, chronic opiates, or additional antidepressants, psychotherapy, electroconvulsive therapy, vagal nerve stimulations therapy, transcranial magnetic stimulation therapy, or phototherapy.

Source of subjects and recruitment methods:
Adult subjects will be recruited from primary care and psychiatry clinics at Brigham and Women's Hospital by physician referral, a brochure, and a poster. Patients presenting to the Brigham Psychiatric Specialties clinic with a chief complaint of depression will be informed of the study during their first appointment. Patients will be under no obligation to enroll in the study; they will have the choice to continue usual care in the clinic or to seek further screening to participate in the study. Subjects will not be recruited from among the investigators' own patients. While some subjects will come from BWH clinics (Psychiatry and Medicine), they will not come from the investigators' panels. Contact information for the study coordinator will be listed on the poster. When subjects contact the coordinator, they will first be asked a series of screening questions as outlined in the screening phone script. These questions will confirm that the patient has a depressed mood, that they are not currently taking antidepressant medication, and that they do not meet one of the basic exclusion criteria.
We will enroll a maximum of 120 patients in order to randomize 42 eligible subjects. Assuming a non-completion rate of approximately 20%, customary in clinical trials of antidepressants, we anticipate 36 completers. With a total of 36 subjects completing the protocol, randomized 1:1 to each arm, the study will be powered to detect a clinically-significant difference of 3.5 units on the HDRS between the groups, assuming α=.05 and β=.8.

IV. SUBJECT ENROLLMENT

Subjects will be adults with major depression seeking treatment, recruited from primary care and psychiatry clinics at Brigham and Women's Hospital by physician referral, a brochure, and a poster. Patients presenting to the Brigham Psychiatric Specialties clinic with a chief complaint of depression will be informed of the study during their first appointment. Demographics will reflect the referral patterns of the participating centers. Subjects may also be recruited through newspaper advertisement, flyers, internet announcements. Contact information for the study coordinator will be listed on the poster. When subjects contact the

coordinator, they will first be asked a series of screening questions as outlined in the screening phone script. These questions will confirm that the patient has a depressed mood, that they are not currently taking antidepressant medication, and that they do not meet one of the basic exclusion criteria.

Given the gender distribution in the prevalence of depression, it is expected that approximately 2/3 of the sample size will be female and 1/3 will be male.

Eligible subjects will be randomized to one of two treatment conditions: sertraline + riluzole or sertraline + placebo. Study staff will instruct the subjects to abstain from alcohol and to report any changes in their medical condition during the study period. Subjects will be reminded to avoid any additional psychiatric care during the study, and to contact staff with any concerns or questions.
The randomization and assignment of the subjects will be done by the Brigham and Women's Hospital Investigation Drug Service (IDS). The pharmacy will assign each subject to sertraline + riluzole or sertraline + placebo.

Details about the study, including objectives, procedures, and potential risks and discomforts will be given in both oral and written form to the subject by the principal investigator (Dr. David J. Wolfe) or a physician co-investigators Dr. Jane L. Erb and Dr. Arthur Joseph III Barsky. Subjects will be given the opportunity to ask any questions and will be given ample time to consider whether they wish to participate. They will be informed that refusal to participate will not interfere with their subsequent medical care.

V. STUDY PROCEDURES

The study design represents a two-arm, randomized, placebo-controlled trial. The primary study interventions are summarized in the schematic and table, below.

Study Visit 1 and 2
At the first study visit, the principle investigator or study physician will obtain informed consent and answer any questions from the subject. Clinical study staff will then administer the Structured Clinical Interview for DSM Disorders to confirm a diagnosis of major depressive episode, and to rule out diagnoses of exclusion. If there are no exclusions at that point, the study staff will administer the HDRS, the Hamilton Anxiety Rating Scale (HARS), the Clinical Global Impressions (CGI) scale. These measures are all customary for clinical trials of antidepressant medication. Subjects with active suicidal ideation, represented by a score of >2 on HDRS item 3, will be ineligible for the study and referred for urgent or emergent clinical assessment as indicated in the safety plan, to rule out potential safety risks and medical causes of depression. All subjects will then have blood tests to assess liver and thyroid function, as well as a urine toxicology

screen. Women of childbearing age will also receive a qualitative urine pregnancy test. All laboratory testing will occur at the Brigham and Women's Center for Clinical Investigation.

Eligible subjects will be randomized to one of two treatment conditions: sertraline + riluzole or sertraline + placebo. Study staff will instruct the subjects to abstain from alcohol and to report any changes in their medical condition during the study period. Subjects will be reminded to avoid any additional psychiatric care during the study, and to contact staff with any concerns or questions. give you a study diary to fill out at home each day. Subjects will be given a study diary to take home with them, where they will write down the time they take the study drug, how much of the study drug they take and whether they have any side effects.

Subjects will be randomized to one of the treatment groups based on a randomization schedule provided by the Brigham & Women's Hospital Investigational Drug Service (IDS) pharmacist assigned to the study. The pharmacy will assign each subject to sertraline + riluzole or sertraline + placebo. All subjects will begin at a 50 mg daily oral dose of sertraline, and for the experimental subjects, riluzole 50 mg twice per day (oral). Consistent with established clinical practice, as well as antidepressant trials employing variable dosing strategies, the sertraline will be increased to 100 mg daily if the subject tolerates the 50 mg daily dose. In event of adverse reactions attributable to the sertraline, the dose will be reduced to 50 mg.

Study visits 3 - 6

In the subsequent four study visits, conducted at two-week intervals, the subject will receive repeat screening with the HDRS, HARS, CGI and SAFTEE. Following currently-recommended clinical guidelines for riluzole, on week 4 following treatment initiation, subjects will have a repeat serum test for liver function. Using a more conservative safety limit than that recommended in clinical practice, any subjects at that point with an ALT >2 times the upper limit of normal will be instructed to discontinue the riluzole and receive placebo instead. The subject will be informed of the change as the protocol requires an additional check of liver function at the end of the study. In that case, the liver function tests will be repeated at week 8 to ensure that the values have normalized.

At each study visit, the study staff will enter the data into case report forms on RedCap. All laboratory values will be reviewed by the Principle Investigator or another physician co-investigator. All study data will be stored securely on RedCap and de-identified prior to data analysis and only group data will be reported. Paper files for each subject, including the consent form, screening materials, subject medication diaries, and any additional correspondence will be

stored in a locked filing cabinet in the office of the Principle Investigator at Brigham and Women's Hospital.

VI. BIOSTATISTICAL ANALYSIS

The baseline data to be collected and analyzed are: subject age at enrollment, age of onset of first depressive episode, gender, number of previous antidepressant medication trials, and number of past depressive episodes, CGI, HARS, and HDRS. Subsequent, repeated measures for analysis will be CGI, HARS, and HDRS. The planned study end-point is at eight weeks after randomization, and is not based on any pre-determined treatment response. All analyses will compare values between the two treatment arms.

Baseline measurements for continuous variables (e.g., age of onset, lifetime number of depressive episodes, current age) will be assessed by t-test. Categorical measurements, such as gender, will be compared with Fisher's exact test or chi-square as appropriate. For the study outcomes, the absolute change in HDRS, HARS, and CGI will be individually evaluated with analysis of variance (ANOVA), while the proportion of subjects achieving remission (HDRS < 7) and response (HDRS >50% reduced from baseline) of their depression will be compared using Fisher's exact or chi-square as appropriate. All applicable tests will be two-tailed with an alpha set at 0.05.

Assuming a non-completion rate of approximately 20%, customary in clinical trials of antidepressants, we will enroll 42 subjects. With a total of 36 subjects, randomized 1:1 to each arm, the study will be powered to detect a clinically-significant difference of 3.5 units on the HDRS between the groups, assuming α=.05 and β=.8. For subjects who discontinue the trial prematurely, the HDRS, HARS, and CGI values will be treated using the last observation carried forward method.

VII. RISKS AND DISCOMFORTS

Riluzole is an FDA-approved drug. The most common (=5%) adverse events that occurred in the ALS marketing trials in patients treated with riluzole vs placebo were: asthenia (19.2% vs 12.2%, respectively), nausea (16.3% vs 10.6%), lung function decrease (not associated with decreased vital capacity; 10.2% vs 9.4%), headache (7.3% vs 6.6%), rhinitis (6.4% vs 6.3%), hypertonia (6.1% vs 5.9%), abdominal pain (5.1% vs 3.8%), and hypertension (5.1% vs 4.1%). Less common side effects are include: vomiting, abdominal pain, dizziness, depression, pruritis, rhinitis, hypertension, and weight loss. While not strictly contraindicated in the prescribing information, for the purposes of this study, patients with baseline liver disease or interstitial lung disease will be excluded from participating.

Sertraline is an FDA-approved drug. The most commonly reported side effects of this drug are: Constipation (3% to 8%), Diarrhea (13% to 24%), Indigestion (6% to 13%), Nausea (13% to 30%), Nausea and vomiting (2% to 30%), Dizziness (6% to 17%), Headache (25%), Insomnia (12% to 28%), Somnolence (2% to 15%), Tremor (5% to 11%), Abnormal ejaculation (7% to 19%), Reduced libido (up to 11%), Fatigue (10% to 16%). In rare instances, individuals undergoing treatment with antidepressants can experience an increase in suicidal thoughts.

With the blood draws, there are risks of pain and bruising at the phlebotomy site, as well as lightheadedness.

The effect of riluzole and sertraline on an embryo or fetus (developing baby still in the womb), or on a breastfeeding infant, is unknown and may be harmful. Because of these unknown risks, women cannot take part in this study if they are pregnant or are trying to become pregnant.

The assessment of psychiatric history, including depression and substance abuse, can make some people feel uncomfortable. Some may also be especially concerned about the confidentiality of mental health information. The study staffs are individuals trained in mental health assessment, and will make every effort to make the subjects comfortable. All subjects will be assured that their history and responses will be kept confidential within the study, except as required by law, in the case of acute safety concerns, and in the instances detailed in the research consent form.

VIII. POTENTIAL BENEFITS

No benefits can be guaranteed to the study participant.

Since all subjects will be receiving standard antidepressant medication in addition to the experimental drug, it is expected that the majority of subjects who complete the study will achieve a decrease or resolution of their depression symptoms. For subjects assigned to riluzole augmentation, it is hypothesized that this response will be more robust and occur more quickly. The results of this study have the potential to improve the effectiveness and speed of depression treatment, as well as better inform our knowledge in the role of glutamate in the pathophysiology of the illness.

IX. MONITORING AND QUALITY ASSURANCE

Since riluzole and sertraline are both approved by the FDA, a Data and Safety Monitoring Board is not required for this study. The principal investigator, Dr. David Wolfe, will be responsible for monitoring the safety of all subjects. In the

event that Dr. Wolfe is unavailable, co-investigators Dr. Jane L. Erb and Dr. Arthur Joseph III Barsky will be available to monitor the safety of all subjects.

Study safety meetings, including the principal investigator, study coordinators, and study physicians will meet every other week to review the current subjects and any reported side effects.

In general terms, a subject will be discontinued from the study for the following reasons:
(1) The subject has experienced an adverse event that, in the opinion of the principal investigator requires early termination,
(2) The subject becomes a safety risk at any time during the trial,
(3) The subject withdraws consent.

Specific to this study, subjects will be closely monitored for adverse events and suicidal thoughts at every visit, and for changes in liver function at 4 weeks. Safety labs (i.e. liver function tests) will be repeated at week 8 for subjects whose tests at week 4 exceeded the pre-determined safety limit of an ALT >2 times the upper limit of normal. In line with usual clinical practice, repeat labs are not indicated for all subjects at week 8 (the study endpoint) as any increased values would have been seen before this time.

Subjects who develop active suicidal ideation, represented by a score of >2 on HDRS item 3, will be referred for urgent or emergent clinical assessment. A patient who develops active suicidal thoughts will be urgently evaluated by a study physician (all of whom are psychiatrists). In any case where there are acute safety concerns arising from suicidality (such as a plan or actual intent), the patient will be sent to the BWH Emergency Department for further evaluation under Section 12a. If there are no acute safety concerns based on the urgent evaluation, the patient will be monitored according to protocol and instructed to contact study staff immediately with any worsening in their mood or thinking. The study doctor will review the urgent or emergent safety assessment and determine if the subject can continue in the study. Any subject who requires a level of care exceeding customary outpatient services (i.e., psychiatric hospitalization or participation in a partial hospital program) will be removed from the study. If a subject must be transferred from the study into clinical care, the study physicians will continue to follow the subjects until they are accepted into appropriate, longer-term care, if clinically indicated. If the subject chooses to discontinue the sertraline at the end of the study, the study physician will prescribe a safe taper of the medication, and arrange for appropriate psychiatric follow up, as clinically indicated.

During all portions of this research study, the privacy and confidentiality of all participants will be maintained at all times.
At each study visit, the study staff will enter the data into case report forms on RedCap. All laboratory values will be reviewed by the Principle Investigator or another physician co-investigator. All study data will be stored securely on RedCap and de-identified prior to data analysis and only group data will be reported. Paper files for each subject, including the consent form, screening materials, subject medication diaries, and any additional correspondence will be stored in a locked filing cabinet in the office of the Principle Investigator at Brigham and Women's Hospital.
If an adverse event occurs, or there is an abnormal finding during laboratory testing, that information will be released to the subjects primary physician with the subject's permission and written release.

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