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A double-blind, placebo-controlled, pilot study of riluzole monotherapy for acute bipolar depression

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Abstract

Background—Glutamatergic system abnormalities are implicated in the pathophysiology and treatment of both major depressive disorder and bipolar depression (BDep). Subsequent to studies demonstrating the rapid and robust antidepressant effects of ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, other glutamatergic modulators are now being studied in clinical trials of mood disorders. A previous open-label study found that riluzole, administered in combination with the mood stabilizer lithium, had antidepressant effects.

Methods—We conducted a randomized, double-blind, placebo-controlled trial of riluzole monotherapy for the treatment of BDep. Nineteen subjects aged 18–70 with bipolar disorder currently experiencing a depressive episode were tapered off of excluded medications and randomized to receive riluzole (50–200 mg/day) or placebo for eight weeks. Rating scale scores (Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAM-D), Hamilton Rating Scale for Anxiety (HAM-A), and Young Mania Rating Scale (YMRS)) were obtained weekly.

Results—No significant differences in depressive symptoms were observed between subjects treated with riluzole and those receiving placebo (p=.12). Anxiety scores were significantly lower in the placebo group (p=.046). An interim analysis was conducted that resulted in stopping the study because of futility; no subjects had achieved treatment response.

Conclusions—Although we found no change in severity of depressive symptoms in BDep patients receiving riluzole compared to placebo, this trial was limited by the relatively high number of subject withdrawals and the small sample size. Thus, while riluzole monotherapy did not demonstrate efficacy for BDep, further studies examining riluzole as adjunctive therapy for this disorder may be warranted.

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Keywords

bipolar depression; riluzole; monotherapy; glutamate; antagonist

Introduction

Bipolar depression (BDep) is associated with high illness severity, poor psychosocial outcomes [1; 2] and, commonly, a depressive course of illness [3]. Medications effective for major depressive disorder (MDD), such as tricyclic or serotonergic antidepressants, have limited efficacy for the treatment of BDep [4; 5]. Furthermore, while mood-stabilizing medications such as lithium or valproic acid are traditionally used to treat bipolar disorder (BD), these agents have been shown to possess greater anti-manic than antidepressant efficacy [6]. As a result, BDep has proven difficult to treat successfully, underscoring the need to identify new and effective treatments for this condition.

Evidence from both animal studies [7] and human clinical trials [8; 9] suggests that glutamatergic system abnormalities are implicated in the pathophysiology of mood disorders, and that glutamatergic modulators have considerable therapeutic potential in the treatment of both MDD and BD. With regard to BD in particular, two double-blind, randomized, placebo-controlled trials found that, compared to saline placebo, a single intravenous dose of the glutamatergic modulator ketamine rapidly improved depressive symptoms within 40 minutes in individuals with BDep who were also being treated with a mood stabilizer; the improvement lasted up to three days [10; 11]. In the wake of these encouraging preliminary findings, a number of different candidate glutamatergic modulating drugs have been investigated to better understand the underlying mechanism of antidepressant response.

One such agent, riluzole, is approved by the US Food and Drug Administration (FDA) for delaying neurodegeneration in amyotrophic lateral sclerosis (ALS). The pharmacological action of riluzole involves inhibition of voltage-dependent sodium channels in neurons [12] and the ability to inhibit glutamate release and enhance both glutamate reuptake and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) trafficking [13]. Preclinical studies suggest that these effects appear to occur independently of each other. For example, tetrodoxin, a sodium channel blocker, failed to block the inhibition of glutamate release [14]. However, *in vitro* animal studies demonstrated an association between riluzole administration and accelerated glutamate clearance from the synapse, thereby preventing glutamate release from presynaptic terminals [15; 16].

Riluzole was reported to have antidepressant effects in both open-label trials [17; 18] and controlled studies of individuals with MDD [19]. In BDep, an eight-week, open-label trial of 14 BDep patients who received riluzole (50–200 mg/day) in combination with lithium found significant improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) scores at week two as well as weeks four through eight [20]. The response rate at week eight for the intent to treat sample was 50%; all the patients who responded achieved remission.

We conducted a double-blind, randomized, placebo-controlled trial of riluzole monotherapy to assess the putative antidepressant effects of riluzole monotherapy in individuals with BDep. This study was prematurely discontinued before the full sample was recruited because of the high dropout rate and lack of response.

Materials and Methods

Participants

Male and female patients 18 to 70 years old with a diagnosis of BD, most recent episode depressed without psychotic features as assessed via the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), were eligible to participate. Subjects were eligible if they had an initial MADRS score of ≥ 20 at their first two study visits, were experiencing a depressive episode lasting at least four weeks, and had experienced at least one previous DSM-IV major depressive episode. Exclusion criteria included any diagnosis of schizophrenia or other psychotic disorder; the presence of psychotic features; the presence of a current anxiety disorder; any serious risk of suicide; being pregnant, nursing, or not using an accepted means of contraception; a serious unstable medical illness; clinically abnormal laboratory tests; substance abuse/dependence within the past 90 days; or a documented history of hypersensitivity or intolerance to riluzole.

Study Design

This study was a randomized, double-blind, parallel group trial designed to assess the efficacy and safety of riluzole (50–200 mg/day) compared to placebo in patients with BDep. The study comprised two study periods. In study period I, after consent, subjects underwent a physical exam, electrocardiogram (ECG), vital signs, blood chemistries, liver function tests, hematology profile, urinalysis (including screens for substances of abuse), hepatitis screen, and SCID. All women of childbearing capacity were required to have a negative ß-HCG. Rating scale assessments included the MADRS (the primary efficacy measure), the Hamilton Rating Scale for Depression (HAM-D-17 item), the Hamilton Rating Scale for Anxiety (HAM-A), and the Young Mania Rating Scale (YMRS). The primary analysis examined the difference in MADRS score between the riluzole and placebo groups. The secondary analyses examined anxiety and manic symptoms. Subjects were tapered off of any medications they were receiving and were free of medications with CNS effects for seven days prior to randomization and throughout the entire duration of the study, except for lorazepam as needed (see below). All subjects received a seven-day single-blind placebo lead-in prior to randomization. All subjects were required to have a MADRS score ≥20 at screening and at baseline of study period II.

Study period II consisted of eight weeks of double-blind, acute treatment. All subjects who met entry criteria were randomized in a 1:1 allocation. Riluzole or placebo was dispensed either once or twice a day as 50 mg tablets or identically appearing placebo pills. Riluzole dosing began at 50 mg by mouth, twice daily, and was increased on a weekly basis by 50 mg, as tolerated, to achieve a maximum total daily dose of 200 mg/day. Dose escalations continued until one of the following occurred: 1) achievement of the primary endpoint (response), 2) intolerable side effects, or 3) completion of the eight-week study. Agitation or

anxiety symptoms were managed with PRN lorazepam (up to 2 mg/day) through the entire duration of the study.

Assuming a response rate to placebo of 20% in patients randomized to placebo and a response rate to riluzole of 60%, a sample size of 60 (30 in each group) was expected. This calculation was based on a two-tailed alpha equal to .05 and provided power of .91. An interim analysis was conducted that resulted in stopping the study because of futility; none of the subjects had achieved treatment response.

Statistical Analysis

A linear mixed model was used with drug, visit, and their interaction as fixed factors. All subjects with a baseline MADRS total score and at least one post-baseline MADRS total score were included in the analysis. Baseline score was a covariate. Restricted maximum likelihood estimates and a compound symmetry covariance structure were used. Subject was a random factor. Given the number of dropouts, secondary models excluded the last two visits to provide more reliable estimates. Significant omnibus effects were examined using Bonferroni post-hoc tests. Significance was evaluated at $p \leq .05$, two-tailed. Similar analyses were run using the HAM-A and the YMRS.

A subject was considered to have responded to riluzole if total MADRS score decreased by ≥50% from baseline to endpoint. We planned to compare the proportion of subjects in each treatment group who met response criteria using a chi-square test.

Results

Nineteen subjects were randomly assigned to receive riluzole (n=8) or placebo (n=11). Table 1 shows the baseline characteristics of the two groups. The mean daily dose of riluzole for subjects in the active drug group was 140.6 mg (88% achieved a dose of 150 mg/day or more). Eight subjects (riluzole n=4, placebo n=4) required PRN benzodiazepine administration during the study.

Ten subjects (five who received riluzole and five who received placebo) did not complete the eight-week treatment phase, though five of those dropped out after six weeks of treatment. In the placebo group, three subjects withdrew due to worsening of depressive symptoms, one withdrew due to headache/irritability, and one withdrew due to influenza. In the riluzole group, two subjects withdrew due to worsening of depressive symptoms, one withdrew due to decreased hematocrit, one withdrew due to increased creatinine kinase, and one developed hypomanic symptoms.

The main finding of this interim analysis was that no subject met response criteria. Using all available data and the primary outcome measure (MADRS), a linear mixed model showed no significant drug effect ($F_{1,16}=3.36$, $p=.09$) and no interaction between drug and time ($F_{7,74}=0.99$, $p=.45$). The mean scores were non-significantly lower in the placebo group than in the riluzole group. Given the number of dropouts, the model was re-run excluding the last two time points, but results indicated that data from this model were in the same direction and had a similar outcome, namely that there was no significant drug or drug by time effect

(Drug: $F_{1,14}$=2.78, p=.12; Drug × Time: $F5_{,63}$=1.15, p=.34). The original statistical model using the HAM-D obtained similar results (Drug: $F_{1,16}$=2.69, p=.12; Drug × Time: $F_{7,73}$=1.04, p=.41), and the findings were the same when eliminating the last two points (Drug: $F_{1,14}$=2.78, p=.12; Drug × Time: $F_{5,63}$=1.15, p=.34).

Models for anxiety and manic symptoms were also run. While no significant differences were seen with the YMRS (Drug: $F_{1,16}$=2.10, p=.17; Drug × Time: $F_{7,74}$=1.64, p=.14), there was a significant drug main effect—but no interaction—with the HAM-A (Drug: $F_{1,15}$=4.74, p=.046; Drug × Time: $F_{7,73}$=1.04, p=.41). Patients receiving placebo had significantly less anxiety.

Discussion

Despite open-label studies suggesting that riluzole may be effective in treating BDep, this randomized, placebo-controlled trial of riluzole monotherapy found that riluzole was not more effective than placebo at any time point. While the average scores appeared numerically lower for placebo compared to riluzole at several time points, no significant differences were noted. In addition, although anxiety scores were significantly lower in the placebo group, at baseline this group was found to be have fewer diagnoses of comorbid anxiety disorder than the riluzole group. Most subjects (13 of 19, and six of eight in the active group) had BD-II, not BD-I. Thus, it is possible that a differential response of BD-I vs BD-II to riluzole, as has been shown with other treatments [4; 21], may have contributed to the negative finding in this study.

The main limitations of the study are the relatively high number of subject withdrawals and the small sample size. However, it should be noted that the high number of withdrawals was at least partly due to the lack of efficacy of riluzole monotherapy without concomitant mood stabilizing medications. The use of PRN benzodiazepines (which was allowed in the study protocol) by eight subjects provides further evidence of the challenge of maintaining subjects in this protocol.

A previous open-label study from our laboratory found that riluzole, administered in conjunction with lithium, had antidepressant properties [20]. In that open-label study, the mean daily dose of riluzole was 171.4 mg. Compared to the lower mean daily dose used in the current monotherapy study (140.6 mg/day), the findings suggest that co-administration of lithium may be required to provide mood stabilization in order to achieve higher effective doses with riluzole and/or to facilitate riluzole's antidepressant effects. Further studies examining riluzole as adjunctive therapy in combination with mood stabilizing treatments for BDep may be warranted.

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dehydronorketamine, and other stereoisomeric dehydro and hydroxylated metabolites of *(R,S)*-ketamine metabolites in the treatment of depression and neuropathic pain. Dr. Zarate is listed as co-inventor on a patent application for the use of *(2R,6R)*-hydroxynorketamine and *(2S,6S)*-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and post-traumatic stress disorders; he has assigned his patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government.

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Table 1

Baseline Characteristics

	Riluzole (n=8)		Placebo (n=11)		
	Mean	**SD**	**Mean**	**SD**	**p**
Age	45.25	15.46	47.64	11.11	0.70
Age of Onset	21.75	5.99	17.45	9.28	0.27
	n	%	n	%	p
Gender (Male)	7	88	6	55	0.13
Current or Past History of Comorbid Diagnosis					
Anxiety Disorder	6	75	3	27	0.04
Eating	1	13	1	9	0.81
Current or Past History of Alcohol/Substance Abuse or Dependence	5	63	5	50	0.60
Bipolar Subtype (BD-I)	2	25	4	36	0.60