References


An Open-Label Trial of Riluzole in Patients With Treatment-Resistant Major Depression

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Objective: This study was conducted to determine the efficacy and safety of riluzole, a glutamate-modulating agent, in patients with recurrent major depression.

Method: After a 1-week drug-free period, subjects 18 years or older with a diagnosis of recurrent major depression and a Montgomery-Åsberg Depression Rating Scale score ≥20 received riluzole monotherapy (100–200 mg/day) openly for 6 weeks.

Results: Nineteen treatment-resistant depressed patients, 53% of whom were classified as having stage 2 treatment resistance or greater, received riluzole at a mean dose of 169 mg/day. Significant improvement occurred during weeks 3 through 6 for all patients and weeks 2 through 6 for completers.

Conclusions: Although preliminary, these results indicate that riluzole may have antidepressant properties in some patients.

I n recent years, there has been growing appreciation that the original monoamine hypotheses do not fully account for the neurobiology of depression or the mechanisms of action of effective treatments. Several lines of research implicate the glutamatergic system in the pathophysiology and treatment of depression, including the delayed, indirect effects of many antidepressants on the glutamatergic system (1), as well as the antidepressant effects of N-methyl-D-aspartate receptor antagonists in animal models of depression (2) and in humans (3). It is also noteworthy that lamotrigine, which inhibits glutamate release, has antidepressant effects in humans (4). Furthermore, there is increasing evidence that mood disorders are associated with regional reductions in CNS volume, possibly resulting from impairments of structural plasticity and cellular resilience (reviewed in reference 5). Notably, the...
Method

The treatment of recurrent major depression.

The glutamatergic system has been implicated in regulating neuronal plasticity and cellular resilience in a variety of neuropsychiatric disorders.

Glutamate-mediated impairments of plasticity have been implicated in neurodegenerative diseases, and several treatment strategies have been implemented to reduce excess CNS glutamate in these diseases (6). One approach involves the use of riluzole, a glutamate-modulating agent (7), which is approved by the Food and Drug Administration for the treatment of amyotrophic lateral sclerosis (8).

The objective of this study was to determine the efficacy and safety of the glutamate-modulating agent riluzole in the treatment of recurrent major depression.

Results

Of 26 subjects screened, 19 patients (nine men and 10 women; mean age=43.1 years, SD=11.7) entered the study, the majority of whom were outpatients (73.7%). The patients received riluzole at a mean dose of 168.8 mg/day (SD=27.2) (84.2% took a dose of 150 mg/day or more) for a mean duration of 5.4 weeks (SD=3.7). The mean age at onset of the illness was 23.9 years (SD=12.6), the mean number of lifetime episodes of depression was 8.5 (SD=11.3), and the mean duration of the current episode of depression was 5.4 months (SD=3.7). Most of the patients were of stage 2 or greater treatment resistance (stages 1=47%, 2=31%, 3=11%, 4=0%, and 5=11%). Two subjects had previously failed to respond to lamotrigine therapy.

Sixty-eight percent (N=13) of the subjects completed the 6-week trial. The reasons for discontinuation were adverse events (N=3) (one with increased values on a test of liver function, one with malaise, and one with nausea and vomiting), nonresponse (N=2), and withdrawn consent (N=1). Data were analyzed on an intent-to-treat basis. Dunnett’s multiple range test was used to compare weekly ratings to those at baseline. Significant improvement in score on the Montgomery-Åsberg Depression Rating Scale from baseline, and clinical remission was defined as a decrease in score on the Montgomery-Åsberg Depression Rating Scale of at least 20% over 6 weeks. A significant difference between groups (p<0.05, Dunnett’s multiple range test).

FIGURE 1. Mean Change in Total Score on the Montgomery-Åsberg Depression Rating Scale From Baseline in Patients With Treatment-Resistant Major Depression Who Were Treated With Riluzole

All patients (N=19)

Trial completers (N=13)

a Significant difference between groups (p<0.05, Dunnett’s multiple range test).
verity scale and Hamilton anxiety scale scores also improved significantly in weeks 3 through 6 for all patients (F=6.75, df=1.9, 34, p=0.04) and trial completers (F=7.62, df=2.0, 24, p=0.003, and F=5.77, df=1.2, 26, p=0.0007) on the CGI severity scale and Hamilton anxiety scale, respectively. The Hamilton anxiety scale score decreased from a baseline mean of 19.3 (SD=7.7) to a mean of 13.8 (SD=9.4). Response rates (50% decrease in score on the Montgomery-Åsberg Depression Rating Scale) at week 6 for all patients and trial completers were 32% and 46%, respectively. Remission rates (score on the Montgomery-Åsberg Depression Rating Scale <10) at week 6 for all patients and completers were 21% and 31%, respectively. Age, gender, clinical features, and dose of riluzole had no effect on change in scores on the Montgomery-Åsberg Depression Rating Scale. Response rates were higher in subjects receiving a dose of 150 mg/day (response rates at 100 mg/day were one-third [33%]; at 150 mg/day, one-half [50%]; and at 200 mg/day, one-eighth [13%]), although these differences were not statistically different. There were no differences in demographic or clinical variables between responders and nonresponders.

The most common adverse events during the trial were headache (58%), gastrointestinal distress (nausea or vomiting) (43%), decreased salivation (47%), constipation (32%), and tension or inner unrest (26%); similar side effects have been observed with riluzole in trials of patients with amyotrophic lateral sclerosis (8). No serious adverse events were noted. One subject was dropped from the study because of an increase in values in liver function tests to three times the upper normal limit. This subject was asymptomatic for hepatic dysfunction, and liver function values returned to normal shortly after discontinuation of riluzole. There was no relationship between the dose of riluzole and adverse events or changes in laboratory test values.

Discussion
In this open-label study, riluzole was associated with antidepressant effects in individuals with treatment-resistant major depression. The response and remission rates in the present study are comparable to those of other antidepressants in studies of treatment-resistant depression (13, 14).

Riluzole has been postulated to exert its effects on the glutamatergic system by means of two distinct mechanisms: through the inhibition of voltage-dependent sodium channels, resulting in the reduction of glutamate release, and also by means of indirect effects on α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid/kainate receptors (7, 15). Furthermore, recent cell culture studies have suggested that riluzole may also exert neurotrophic effects by stimulating the synthesis of brain-derived neurotrophic factor (16). Although studies to ascertain if similar effects occur in vivo have not yet been undertaken, these findings are particularly noteworthy since conventional antidepressant treatments have been shown to increase the expression of brain-derived neurotrophic factor in the rat hippocampus and the infusion of intrahippocampal brain-derived neurotrophic factor produces antidepressant effects in preclinical behavioral models of depression (17).

It is clear that our preliminary results need to be interpreted with caution given the small group size and the open-label nature of the study. Nevertheless, the significant and often striking response seen in some individuals who were refractory to traditional monoamine antidepressants suggests that direct modulation of the glutamatergic system may have considerable use for the treatment of mood disorders. Larger controlled studies are needed to confirm these preliminary findings.

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