



Developing Therapeutic Alternatives for Treatment-resistant Bipolar Depression: The Role of Riluzole

Tedavi Dirençli Bipolar Depresyonda Gelişen Tedavi Seçenekleri: Riluzol

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Dear Editor,

Bipolar disorder (BD) refers to a set of conditions characterised by depressive, manic, or hypomanic episodes. This chronic psychiatric disease affects 2.4% of the adult population in the United States of America (0.6% BD-I, 0.4% BD-II and 1.4% sub-threshold BD).¹ The treatment primarily involves administration of mood-stabiliser medications such as lithium and valproate. Additional options include psychotherapy and the prescription of atypical anti-psychotics.² However, the rise in the number of treatment-resistant bipolar depression cases has prompted the investigation of N-methyl-D-aspartate (NMDA) receptor antagonists. This interest has been sparked by reports on abnormalities related to glutamatergic neurotransmission in studies involving animal and human subjects.^{3,4} Such defects include the presence of elevated levels of glutamate in the plasma and cerebrospinal fluid, alterations in the NMDA-receptor binding, defects in the genetic expression in areas associated with long-term potentiation and diminished expression of certain metabotropic glutamate receptors (GluR2 and GluR3).³ Promising preliminary results obtained upon ketamine administration have encouraged the investigation of riluzole, a potent NMDA antagonist approved by the Food and Drug Administration, for the treatment of amyotrophic lateral sclerosis through delayed neuronal degeneration.^{5,6}

In a double-blind, placebo-controlled, randomised controlled trial (RCT) involving 19 subjects diagnosed with BD (age: 18-70 years), the patients were randomised into either placebo or 50-200 mg riluzole group for an 8-week observation period. The riluzole group showed statistically significant lower anxiety scores than the placebo group, as assessed by the Hamilton Rating scale for anxiety, and no difference in the depression scores, as assessed by the Montgomery-Åsberg Depression

Rating scale (MADRS) and Hamilton Rating scale for depression. A total of 10 participants (5 in the placebo group and 5 in the riluzole group) did not complete the 8-week trial course (3 placebo group patients withdrew from the participation owing to the following reasons: one due to deterioration of depressive status, one due to severe headache and another due to influenza infection).⁷ Although RCT did not favour riluzole therapy for bipolar depression, we believe that our study results were challenged by the limitations of small sample size, participant withdrawals and the relatively short period of intervention. Another study on 14 bipolar cases in which the patients received 50-200 mg riluzole for 8 weeks in case of MADRS score ≥ 20 after 4 weeks of treatment with lithium also demonstrated the beneficial effects of riluzole for bipolar depression treatment. No manic or hypomanic episodes were recorded during the course of riluzole therapy.⁸ In general, no intolerable adverse effects were observed.^{7,8} In addition, a past study on 19 adult patients with non-bipolar treatment-resistant major depression (MADRS score ≥ 20) revealed significant improvements with riluzole treatment (mean dosage =169 mg/day) for 6 weeks.⁹ However, the efficiency of riluzole was limited in ketamine-resistant major depression cases and hence the combination therapy of riluzole with ketamine was deemed to be less effective than the use of ketamine alone.^{10,11}

NMDA antagonists have been proven to exert beneficial effects in treatment-resistant bipolar depression cases with valid pathophysiological background; however, relevant studies in the literature are limited owing to the small sample size and the short intervention and follow-up durations. Hence, there is a need for large-scale and comprehensive RCTs to investigate the efficacy and safety of riluzole treatment in patients with bipolar depression. Moreover, physicians should be aware of such developing areas of psychiatric research which are likely to

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influence clinical practise in the coming years.

Keywords: Bipolar disorder, riluzole, depression, N-methyl-D-aspartate receptor, glutamate

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