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Riluzole combination therapy for moderate-to-severe major depressive disorder: A randomized, double-blind, placebo-controlled trial

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ABSTRACT

Recent evidences suggest that glutamatergic dysregulation implicated in neural plasticity and cellular resilience may contribute to the pathophysiology of Major Depressive Disorder (MDD). Riluzole, which exerts its effect by targeting glutamate neurotransmission, has shown antidepressant effect in recent preclinical, observational and open label studies. This study aimed to assess the efficacy and tolerability of riluzole in patients with MDD. Sixty-four inpatients with diagnosis of moderate to severe major depressive disorder participated in a parallel, randomized, controlled trial, and sixty patients underwent 6 weeks treatment with either riluzole (50 mg/bid) plus citalopram (40 mg/day) or placebo plus citalopram (40 mg/day). All participants were inpatients for the whole duration of the study. Patients were assessed using Hamilton depression rating scale (HDRS) at baseline and weeks 2, 4 and 6. The primary outcome measure was to assess the efficacy of riluzole compared to placebo in improving the depressive symptoms. General linear model repeated measures demonstrated significant effect for time × treatment interaction on HDRS [$F(1.86, 107.82) = 8.63$, $p < 0.001$]. Significantly greater improvement was observed in HDRS scores in the riluzole group compared to the placebo group from baseline HDRS score at weeks 2, 4 and 6 ($p < 0.001$, $p = 0.001$, $p = 0.002$, respectively). Significantly greater response with greater speed to treatment was observed in the riluzole group than the placebo group. No serious adverse event occurred. This study showed a favorable safety and efficacy profile in patients with major depressive disorder. Larger controlled studies with longer treatment periods are needed to investigate long term safety, efficacy and optimal dosing.

1. Introduction

Major depressive disorder (MDD) is a chronic, disabling psychiatric disorder associated with high morbidity and mortality throughout the world. The World Health Organization (WHO) points out that unipolar depressive disorders rank third amongst contributors to the global disease burden (Collins et al., 2011).

Although considerable advances in treatment of depression have occurred, several problems still remain. Available treatments are associated with a large number of adverse effects. In addition, substantial proportion of MDD patients do not adequately respond to their first medication and existing treatments are associated with clinically significant lag time to onset of therapeutic efficacy, which is associated with significant morbidity and suicidal risk (Ates-Alagoz and Adejare, 2013; Lapidus et al., 2013; Mathews et al., 2012; Zarate et al., 2010). Resistant patients are usually managed by switching treatment to another medication or augmentation therapy. Recently, there is growing evidence for combination therapy as initial treatment to achieve greater and quicker response. However, studies in support of this notion have not been definitive (Sepanjnia et al., 2012; Shelton et al., 2010).

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Most MDD pathophysiology etiological theories used to focus on brain modulatory monoamine systems (dopamine, serotonin and norepinephrine). A more recent line of evidence points to glutamate, the brain's principal excitatory neurotransmitter, as playing a role in MDD's pathophysiology. Additionally, glutamate dysregulation is known to cause impairments in structural plasticity and cellular resilience, which seems to be implicated in mood disorders as well (Pittenger et al., 2008; Zarate et al., 2003; Zarate and Manji, 2008). It is therefore reasonable to hypothesize that medications which reduce glutamatergic tone may be able to play a role in treatment of depression. One candidate drug is riluzole which has antiepileptic, neuroprotective, and modulatory properties on the glutamatergic neurotransmission. Clinical evidence from several, mostly open label and observational studies, have suggested efficacy of riluzole in treatment of unipolar or bipolar depression and treatment-resistant major depression (Brennan et al., 2010; Sanacora et al., 2004, 2007; Singh et al., 2004; Zarate and Manji, 2008; Zarate et al., 2004, 2005). Riluzole appears to cause no adverse effect on hippocampal plasticity, sparing episodic and visuospatial memory, thus mitigating a theoretical concern regarding its use in the elderly (Sasaki-Hamada et al., 2013).

Based on the available data, we hypothesized that riluzole might be an appropriate augmentative option for improving depressive symptoms, considering its modulatory properties on the glutamatergic neurotransmission and its acceptable safety. Therefore, a randomized, placebo-controlled trial was designed to assess the safety and efficacy of riluzole in combination with citalopram, as a standard of care agent, in improving depressive symptoms in MDD patients. Since our subjects were inpatients, we administrated riluzole and citalopram simultaneously for feasibility of the study process and to decrease the duration of hospitalization. However, in the clinical practice, it would be more practical to consider administration of riluzole in patients who are non-responder or partial responders to standard therapeutic agents.

2. Patients and methods

2.1. Trial design and setting

This 6-week, two-center, randomized, double-blind, placebo-controlled, parallel-group trial was performed between March 2014 and March 2015, in the inpatient clinic of Roozbeh Psychiatric Hospital affiliated with Tehran University of Medical Sciences (TUMS) and Razi Psychiatric Hospital affiliated with the Welfare and Rehabilitation University. The study was approved by the institutional review board (IRB) of TUMS (Grant No: 22192), and was performed consistent with Declaration of Helsinki and its subsequent revisions. Written informed consent was obtained from all eligible participants following complete description of study details. Participants were informed that they were free to withdraw from the trial anytime without any negative effect on their therapy. The trial was registered at the Iranian registry of clinical trials (www.irct.ir; registration number: IRCT201307181556N54).

2.2. Participants

Male and female inpatients between 18 and 50 years of age with diagnosis of major depressive disorder based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) were included in this study as verified by the Structured Clinical Interview for DSM-IV axis-I disorders/patients edition (SCID-I/P). Patients were required to have a score of at least 19 on the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and a score of 2 or more on item 1 of HDRS. Citalopram was the drug of choice for patients regardless of other eligibility criteria. Exclusion criteria included: Presence of psychosis, any other mental disorder on DSM-IV axis I (Subjects were excluded if they had another Axis I disorder as a principal diagnosis in the 6 months prior to screening. Comorbid Axis I diagnoses of anxiety disorders were permitted if they were not the primary focus of treatment within 6 months before trial), suicidal ideation (score > 2 on the suicide item of the HDRS, or those who were judged to have substantial risk of suicide by the physician), mental retardation (intelligence quotient < 70 based on clinical judgment and reviewing prior neurocognitive testing and records), any antidepressant use during the last one month or electroconvulsive therapy (ECT) during the last two months, or use of any psychotropic medication during the last three months, alcohol or substance (with the exception of nicotine) dependence, existence of serious or life-threatening medical conditions, presence of hypothyroidism, cardiovascular problems, rising liver transaminases to three times the upper limit of normal or higher, pregnancy and lactation.

2.3. Intervention

Eligible participants were randomly assigned to receive either 50 mg Riluzole bid (Rliutek; Sanofi-Aventis, 50 mg tablet) daily or placebo tablets, in the same manner, for six weeks. All patients, regardless of their assigned group, received 20 mg/day citalopram for the first week and 40 mg/day for the subsequent 5 weeks. Participants were not allowed to undergo any behavioral intervention therapy or use any psychotropic drugs or undergo ECT during the course of the trial.

2.4. Outcome

All participants were evaluated using HDRS at baseline and weeks 2, 4 and 6. HDRS is a validated 17 item (on a three-point or five-point scale) rating scale which evaluates the severity of depressive-related symptoms (Hamilton, 1960). HDRS has been used to assess treatment efficacy and severity of depressive symptoms in several clinical trials in Iran (Abbasi et al., 2015; Emadi-Kouchak et al., 2016; Jafari et al., 2015; Mohammadinejad et al., 2015; Zeinoddini et al., 2014, 2015). Two psychiatrists with previous experience in this field conducted all assessments and the inter-rater reliability (intra-class correlation coefficient) between the two raters was >0.90. The primary outcome measure of this trial was evaluation of riluzole efficacy in improvement of depressive symptoms compared to placebo using general linear model repeated measures. Two groups were also compared with respect to the reduction in HDRS scores from baseline at each time point, early improvement (≥20% reduction in HRDS score within the first two weeks), response to treatment (≥50% reduction in the HDRS score), remission rate (HDRS score ≤ 7) and the time needed to respond to treatment.

2.5. Safety

Patients were asked to immediately inform the research team about any unexpected symptom or complaint during the course of the trial. All patients underwent a thorough physical examination at the screening session and at each visit. All participants were systematically asked for adverse events at each visit through open-ended questioning followed by a complete side effects checklist (a 25-item checklist). Furthermore, complete blood count (CBC) was obtained and serum aminotransferases were measured at baseline and weeks 0, 3 and 6.

2.6. Sample size

Assuming a mean difference of 4 on the HDRS score between the riluzole and the placebo groups, with a standard deviation of 4 (based on our pilot study) and a power of 95% and a two-tailed significance level of 0.05, a sample size of 54 was calculated. Assuming a 15% attrition rate, a total sample size of 64 was needed.

2.7. Randomization, allocation concealment, and blinding

Randomization was performed by the permuted randomization block method using a computerized random number generator by an independent party (allocation ratio 1:1, blocks of four). Allocation concealment was performed using sequentially numbered, sealed, opaque, and stapled envelopes. An aluminum foil inside the envelope rendered the content of envelope impermeable to intense light. Riluzole and placebo tablets were identical in their size, shape, color, texture and odor. The patients, the nurses, the physician who referred the patient, the investigator, and the raters were all blinded to treatment allocation. At the end of the trial, we asked patients, nurses and the raters whether they thought they were on active treatment or placebo.

2.8. Statistical analysis

Frequency (%) of categorical variables and mean ± standard deviation (SD) of continuous variables is reported. General linear model repeated measure was used to compare HDRS scores between the two groups during the course of the trial. Greenhouse–Geisser correction was used for degrees of freedom whenever Mauchly's test of sphericity was significant. Independent T-test was used to compare reduction in HDRS scores from baseline to each study point between the treatment groups and Cohen's d was calculated. To compare categorical variables between the two groups, chi square test and Fisher's exact test were used. Laboratory values were compared between the two groups using the independent T-test. To compare the time needed to respond to treatment between the treatment groups, the *Kaplan–Meier* estimation with log-rank test was used. Considering ≥50% reduction from baseline HDRS score to week 6, as the response to the riluzole combination treatment, the number needed to treat (NNT) was measured. Statistical analysis was conducted using Statistical Package of Social Science Software (SPSS version 20, IBM Company, USA). Graph of repeated measure test was drawn using sigma plot (version 12).

3. Result

3.1. Participants

A total of 82 participants were screened for eligibility criteria, among whom 64 patients were included in the study and were randomized to receive either riluzole (n = 32) or placebo (n = 32). Sixty patients completed the study and participated in all follow-up visits and their data was included in the analysis (Fig. 1). Baseline characteristics of the participants as well as their baseline HDRS scores were not significantly different between treatment groups (Table 1). There was no significant difference in laboratory values between the two groups at baseline and at weeks 3 and 6 (Table 2).

3.2. Outcomes

3.2.1. HDRS score

There was no significant difference in baseline HDRS scores between the riluzole and the placebo group (24.43 ± 2.14 vs. 23.63 ± 3.61, respectively, [MD (95% CI) = 0.80 (−0.74 to 2.33), t (47.16) = 1.04, p = 0.30])). General linear model repeated measures demonstrated significant effect for time × treatment interaction on the HDRS score [F (1.86, 107.82) = 8.63, p < 0.001] (Fig. 2). Significantly greater improvement was observed in the HDRS scores of the riluzole group compared to the placebo group from baseline to weeks 2, 4 and 6 (p < 0.001, p = 0.001, p = 0.002, respectively (Table 3). Significantly greater early improvement rate was observed in the riluzole group (93.3%) than the placebo group (53.3%) (p = 0.007) (Table 4). Significantly greater response rate was observed in the riluzole group compared to the placebo group at weeks 4 and 6 (Table 4). Remission rate was greater in the riluzole group than the placebo group (26.7% vs. 10%). However, the difference did not reach statistical significance (Table 4). *Kaplan–Meier* estimation demonstrated that a shorter time was needed in the riluzole group than the placebo group for response to treatment (p < 0.001). The baseline HDRS scores were not statistically different between patients in two centers. Furthermore, the mean reduction in HRDS score from baseline to the study end, was not statistically different between patients of two centers in each groups.

3.2.2. Adverse events

The frequency of adverse events was not significantly different between riluzole and placebo (Table 5). No serious adverse event and no death occurred. CBC elements and serum aminotransferase levels were not significantly different between the treatment groups during the study and at trial conclusion (Table 2).

3.3. Blinding

The patients and the raters guessed wrongly about the allocated treatment in more than 50% of allocations.

4. Discussion

To the best of our knowledge this is the first randomized placebo-controlled trial which explores the efficacy of riluzole in the combination therapy of MDD. The results of the current study demonstrated administration of riluzole, in combination with citalopram, is significantly superior to citaloperam monotherapy in reducing depressive symptoms and resulted in faster response to treatment in MDD patients for whom citalopram was the drug of choice. The use of riluzole combination therapy also appeared to be safe and well tolerated in this study and no serious adverse event was reported. Uniquely, our findings showed considerably quicker improvements (93.3%) and statistically shorter lag time to the clinical effect onset. Since baseline characteristics of patients were not significantly different at the baseline, the better outcome in the intervention group can be attributed to the probable beneficial effects of riluzole in depression. It is important to note that remission rate with citalopram in the control group of our survey was comparable to remission rates of 10–40% obtained in other trials of citalopram (Khajavi et al., 2012; Maeng and Zarate, 2007).

Our findings are consistent with case studies and series in which efficacy of adjunctive riluzole therapy in MDD or bipolar depression have been reported (Sanacora et al., 2004; Singh et al., 2004). In an open label study of 19 patients with Montgomery Asberg Depression Rating Scale scores (MADRS) of 20 or greater, six weeks of riluzole monotherapy showed similar efficacy to conventional antidepressants. Response and remission rates of 46% and 31% were detected, respectively (Zarate et al., 2004). In another open-label study which was conducted on 14 patients with bipolar depression, riluzole monotherapy was associated with significant improvement in depressive symptoms with a very large effect size

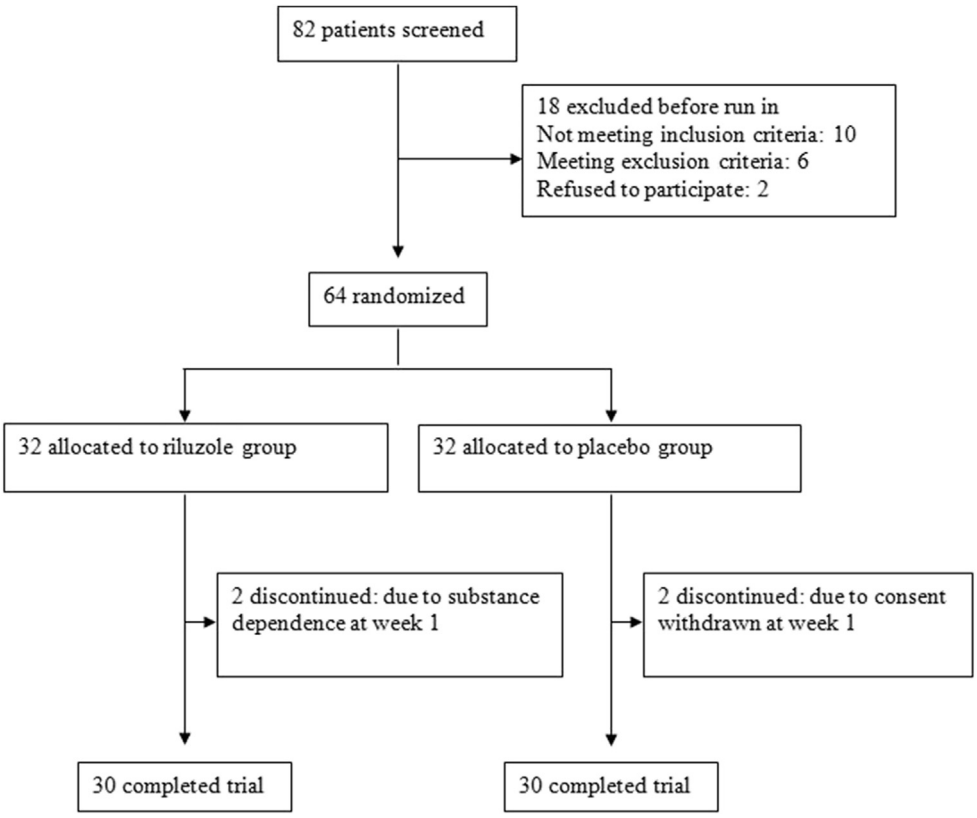

Fig. 1. Flow diagram of the study.

Table 1
Baseline characteristics of the patients according to the treatment group.

	Riluzole group (n = 30)	Placebo group (n = 30)	P-value
Age, year, mean ± SD	34.56 ± 7.23	33.23 ± 7.25	0.48
Gender, M:F, n (%)	22 (73.3%):8 (26.7%)	19 (63.3%):11 (36.7%)	0.40
Duration of illness, months, mean ± SD	2.58 ± 0.88	2.65 ± 1.07	0.79
Smoking, n (%)	20 (66.7.0%)	18 (60.0%)	0.59
Educational level, n (%)			0.85
• Under diploma	5 (16.7%)	4 (13.3%)	
• Diploma	20 (66.7%)	22 (73.3%)	
• University degree	5 (16.7%)	4 (13.3%)	
Weight, kg, mean ± SD	68.50 ± 11.73	70.60 ± 9.04	0.44
Height, cm, mean ± SD	174.1 ± 8.6	170.4 ± 8.10	0.09
Baseline HDRS score, mean ± SD	24.43 ± 2.14	23.63 ± 3.61	0.30
Prior antipsychotic medications, N (%)			NA*
• Citalopram	4 (13.33%)	6 (20%)	
• Fluoxetine	14 (46.66%)	12 (40%)	
• Venlafaxine	7 (23.33%)	6 (20%)	
• Sertraline	8 (26.66%)	9 (30%)	

Abbreviations: n, number; SD, standard deviation; HDRS, Hamilton Depression Rating Scale; M, male; F, female; *: not applicable since some patients received more than one medication.

(cohen's d > 2.0) (Brennan et al., 2010). Sanacora et al. reported results of riluzole adjunctive therapy and compared it to the traditional monoaminergic antidepressants on 13 patients with treatment resistant MDD. At the end of six weeks, riluzole augmentation therapy resulted in significant rapid improvement of depressive symptoms with a 9.6 points reduction in HDRS mean scores, and response and remission rates of 40% and 30%, respectively (Sanacora et al., 2007; Zarate and Manji, 2008). Additionally, an 8 week add-on riluzole therapy on 14 treatment resistant depressed bipolar patients with MADRS ≥20 was well tolerated and its administration resulted in a significant treatment effect without switch into hypomania or mania (Zarate et al., 2005).

The antidepressant effect of riluzole has also been shown in depression animal models of depression. In one experiment using animals exposed to chronic unpredictable stress, a rodent model of depression, cortical glial dysfunction was improved after riluzole administration (Banasr et al., 2010). Dose dependent therapeutic effects were reported on forced swim test and incentive disengagement models of depression which correlated with increased expression of brain derived neurotrophic factor (BDNF) and glial transporter 1 (GLT1) (Gourley et al., 2012). Therefore, higher doses of riluzole may result in more pronounced effects, a point which

Table 2
Laboratory tests at baseline and during the study.

Lab data	Week	Riluzole group	Placebo group	P-value
RBC, $\times 10^{12}$/L, mean (SD)	Week 0	4.2 ± 0.8	4.1 ± 0.7	0.61
	Week 3	4.5 ± 0.7	4.4 ± 0.7	0.71
	Week 6	4.6 ± 0.6	4.5 ± 0.6	0.52
WBC, $\times 10^{9}$/L, mean (SD)	Week 0	8.4 ± 2.5	8.2 ± 1.9	0.73
	Week 3	7.9 ± 2.1	8.4 ± 1.8	0.33
	Week 6	8.5 ± 2.6	8.3 ± 2.0	0.74
HB, g/dL, mean (SD)	Week 0	13.5 ± 2.5	12.6 ± 1.8	0.12
	Week 3	14.6 ± 1.9	13.9 ± 1.6	0.13
	Week 6	13.5 ± 1.9	13.4 ± 1.9	0.84
Hct, mean (SD)	Week 0	39.8 ± 6.4	37.9 ± 6.1	0.24
	Week 3	39.6 ± 7.5	39.1 ± 7.2	0.79
	Week 6	38.4 ± 8.0	38.8 ± 6.5	0.83
AST, IU/L, mean (SD)	Week 0	21.5 ± 8.6	21.4 ± 7.8	0.96
	Week 3	22.6 ± 8.3	21.5 ± 7.6	0.59
	Week 6	22.5 ± 6.6	21.7 ± 6.9	0.65
ALT, IU/L, mean (SD)	Week 0	19.5 ± 7.4	19.8 ± 6.9	0.87
	Week 3	18.9 ± 7.5	19.3 ± 6.6	0.83
	Week 6	19.7 ± 7.2	19.0 ± 6.5	0.69

Abbreviations: RBC, red blood cell; WBC, white blood cell; HB, hemoglobin; Hct, hematocrit; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

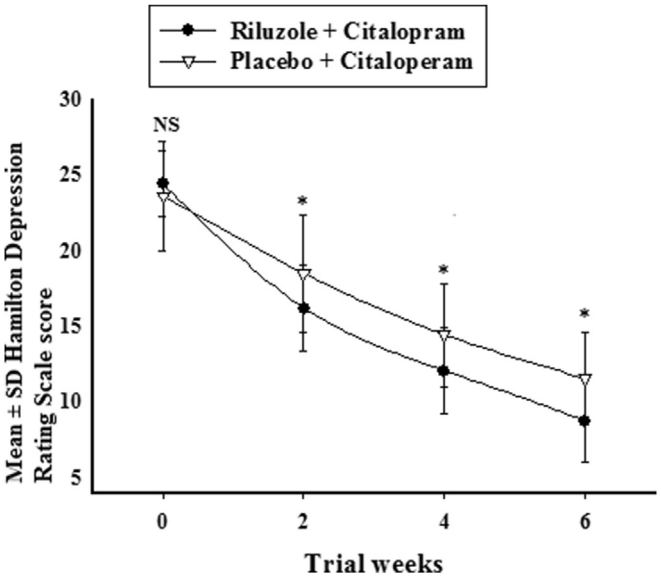

Fig. 2. Repeated measure for comparison of the effects of two treatments on Hamilton depression rating scale (HDRS). Values represent mean ± standard deviation. P-values show the result of the independent t-test comparing of HDRS scores between the two groups at each time point. NS indicates non-significant; *, $p < 0.05$.

demonstrated on imaging and autopsy studies of patients with MDD may relate to the dysregulation of the glutamatergic transmission. There is also evidence for changes in metabolic activity and gene expression profiles which involves glutamatergic neurotransmission in animal models of MDD (Duncan et al., 2013; Hashimoto et al., 2007; Salvadore and Zarate, 2010; Stein et al., 2007; Veeraiah et al., 2014; Zarate et al., 2003).

Riluzole (2-amino-6-trifluoromethoxy benzothiazole) is a glutamatergic modulator with neuroprotective properties approved for the treatment of amyotrophic lateral sclerosis. Although riluzole mechanism of action in mood disorder patients is not fully understood, it is proposed that its efficacy relates to its ability to counteract dysfunctional glutamatergic transmission in MDD. The most important and possible mechanisms to reduce glutamatergic dysfunction by riluzole is proposed to happen through increased glutamate metabolism and transportation, enhanced glutamate uptake by either synaptic neurons or astrocytes, increased affinity of excitatory amino acid transporter (EAATs), increased α-Amino-3-Hydroxy-5-Methyl-4-isoxazolepropionate (AMPA) trafficking by promotion of membrane insertion of glutamate receptors 1 and 2 (GluR1 and GluR2) and activation of neurotrophic factor synthesis considering the brain glutamate concentrations attained by our study dosing. All of these mechanisms are proposed to lead to enhanced neural plasticity by recent investigations. There is increasing evidence suggesting that effective treatment should provide plasticity enhancing strategies along with classical neurochemical support. Besides, it was proposed there are bidirectional interactions between inflammatory mediators, one of the possible reasons of depression, and glutamate in a way which leads to neurotoxicity and induction of depressive symptoms (Doble, 1996; dos Santos Frizzo et al., 2004; Du et al., 2007; Machado-Vieira et al., 2009; Manji et al., 2003; Martin et al., 1993; McNally et al., 2008; Valentine and Sanacora, 2009; Zarate et al., 2010; Zarate and Manji, 2008). Mentioned hypotheses claiming superior therapeutic effects of glutamatergic regulators and advantage of neural plasticity enhancers on depressive symptoms were also powered by successful administration of other drugs with these properties such as ketamine and amantadine in MDD patients (aan het Rot et al., 2010; Ates-Alagoz and Adejare, 2013; DiazGranados et al., 2010; Duncan et al., 2013, Ibrahim et al., 2012; Maeng and Zarate, 2007; Murrough et al., 2013; Owen, 2012).

Although this study was a statistically powered randomized placebo controlled study to explore the efficacy of riluzole as combination therapy in patients with MDD which was blinded at the level of participants, investigators, raters and analyzer, it was not designed to assess and thus interpret statistically significant

Table 3
Comparison of score changes between the two groups using independent T-test.

HDRS score	Riluzole group	Placebo group	Mean difference riluzole-placebo (95% CI)	t	Cohen's d	P-value
Change from baseline to week 2, mean ± SD	8.23 ± 2.34	5.13 ± 3.47	3.10 (1.57–4.63)	4.05	1.06	<0.001
Change from baseline to week 4, mean ± SD	12.37 ± 3.02	9.20 ± 4.03	3.17 (1.33–5.01)	3.44	0.90	0.001
Change from baseline to week 6, mean ± SD	15.67 ± 2.99	12.10 ± 5.09	3.57 (1.40–5.73)	3.31	0.87	0.002

Abbreviations: SD, standard deviation; CI, confidence interval; HDRS, Hamilton depression rating scale.

can be subject of future trials. Our findings are in agreement with the recently proposed role for glutamatergic transmission in mood disorders which is detected by studies of postmortem human brain, plasma and cerebrospinal fluid of patients with mood disorders, magnetic resonance spectroscopy and other brain imaging techniques and gene expression profiles of MDD patients. Additionally impairments of structural plasticity and reduced cellular resilience

differences between the groups in regards to safety issues. Moreover, relatively small sample size and especially short follow-up period prevent us from assessing the true long term effects of riluzole with respect to probability of relapse and side effects of the agent. In addition, fixed dose administration of the drug, which might not be an ordinary routine in everyday practice, and lack of riluzole mechanisms of action evaluation can be other limitations

Table 4
Comparison of outcome indexes between the two groups.

Outcome	Riluzole group (n = 30)	Placebo group (n = 30)	P-value	NNT	Odds ratio
Number (%) of early improvers	28 (93.3%)	16 (53.3%)	<0.001	2.50	12.25
Number (%) of responders at week 2	0 (0.0%)	0.0	–	–	–
Number (%) of responders at week 4	19 (63.3%)	7 (23.3%)	0.002	2.50	5.67
Number (%) of responders at week 6	29 (96.7%)	13 (43.3%)	<0.001	1.87	37.92
Number (%) of remitters at week 6	8 (26.7%)	3 (10.0%)	0.09	5.98	3.27

NNT indicates number needed to treat.

Table 5
Frequency of the adverse events in the two study groups.

Adverse events	Riluzole group	Placebo group	P-value
Drowsiness, n, %	10 (33.3%)	8 (26.7%)	0.57
Constipation, n, %	5 (16.7%)	4 (13.3%)	1.0
Dizziness, n, %	8 (26.7%)	7 (23.3%)	1.0
Abdominal pain, n, %	6 (20.0%)	5 (16.7%)	1.0
Increased appetite, n, %	3 (10.0%)	5 (16.7%)	0.71
Decreased appetite, n, %	3 (10.0%)	2 (6.7%)	1.0
Nausea, n, %	7 (23.3%)	6 (20.0%)	1.0
Headache, n, %	5 (16.7%)	4 (13.3%)	1.0
Dry mouth, n, %	6 (20.0%)	5 (16.7%)	1.0
Cough, n, %	5 (16.7%)	3 (10.0%)	0.71
Diarrhea, n, %	7 (23.3%)	5 (16.7%)	0.52

of our survey.

5. Conclusion

A 6-week course of treatment with riluzole in combination with citalopram showed favorable safety and efficacy profile in patients with MDD. Nevertheless, larger controlled studies with longer treatment periods are needed to investigate long-term safety, efficacy and optimal dosage.

Conflicts of interest

None.

Author contributions

Dr Salardini participated in data acquisition and the preparation of the manuscript. Dr Atefeh Zeinoddini and Dr. Arefeh Zeinoddini performed data analysis and wrote the manuscript. Dr Mohammadinejad participated in the preparation of the manuscript. Dr Khodaie-Ardakani and Dr Zahraei participated in data acquisition. Dr Akhondzadeh designed the manuscript, provided the outlines for the presentation of the study, supervised the study process and edited the final manuscript. All authors have reviewed the process of data analysis, writing of the manuscript and approved the final article.

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