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Review article

Efficacy and safety of riluzole for depressive disorder: A systematic review and meta-analysis of randomized placebo-controlled trials

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ABSTRACT

Glutamatergic modulators may have therapeutic potential in the treatment of depressive disorder (DD), riluzole, as a modulating drug of the glutamatergic system, its antidepressant efficacy and safety of riluzole for DD are inconsistent. This meta-analysis was performed to determine the efficacy and safety of riluzole used for DD.

A systematic literature search was performed using PubMed, Embase, Cochrane Library, Web of Science, VIP and other databases from 1980 to 2019. The primary outcome was change in depression severity and meta-analysis was performed using comprehensive meta-analysis software. Seven randomized controlled trials (RCTs) were included. There was some difference in depression severity change in riluzole-citalopram therapy. No significant differences were observed in response rate, remission rate, relapse rate and adverse events, while, the relapse time in riluzole group was longer than placebo group.

In this meta-analysis riluzole showed no antidepressant efficacy compared to placebo in monotherapy or riluzole-ketamine combined therapy, while it might relieve depression severity to some extent in riluzole-citalopram therapy. Furthermore, riluzole showed favorable safety for DD. The longer relapse time of riluzole group might have clinical significance to some extent, although this had no statistical difference. More studies are needed to clarify the potential association between riluzole and DD.

1. Introduction

Depressive disorder (DD) is the worldwide, leading cause of years lived with disability, accounting for almost 10% of the total disability (Vos et al., 2012; Lim et al., 2018). This devastating disorder imposes a huge economic burden on patients and the healthcare systems (Mrazek et al., 2014). DD is considered as a neurocognitive disorder with associated impairments in adult neurogenesis and neural circuits (Lyall et al., 2019). Therapeutic effects of the currently available antidepressant treatments are limited considering their low response rates and delayed therapeutic effects (Formolo et al., 2019). Several studies suggest that glutamatergic system abnormalities are implicated in the pathophysiology of mood disorders and that glutamatergic modulators have considerable therapeutic potential in the treatment of DD (Prados-Pardo et al., 2019; Lener et al., 2017).

Riluzole, as a modulating drugs of the glutamatergic system, is approved by the US Food and Drug Administration for amyotrophic lateral sclerosis (Liu et al., 2018). Riluzole does not antagonize the N-methyl-Daspartate receptor, and it causes no adverse effect on hippocampal plasticity, sparing episodic and visuospatial memory (Zarate et al., 2010; Sasaki-Hamada et al., 2013).

The efficacy of riluzole for DD is still in controversy. Several previous open-label trials and a recent placebo-controlled trial found that riluzole had good efficacy in patients suffered from major depression and bipolar depression (Pittenger et al., 2008; Salardini et al., 2016). In contrast, one study reported that riluzole lacked efficacy in major depressive disorder patients compared with placebo (Mathew et al., 2017) and another 4-week, placebo-controlled study found that the response rate and relapse time of riluzole did not differ from the placebo group (Ibrahim et al., 2012). Furthermore, in many countries riluzole has not been used to treat DD. The purpose of this study was to systematically review the use of riluzole in DD and assess its efficacy and safety, hoping to promote the progression of this field.

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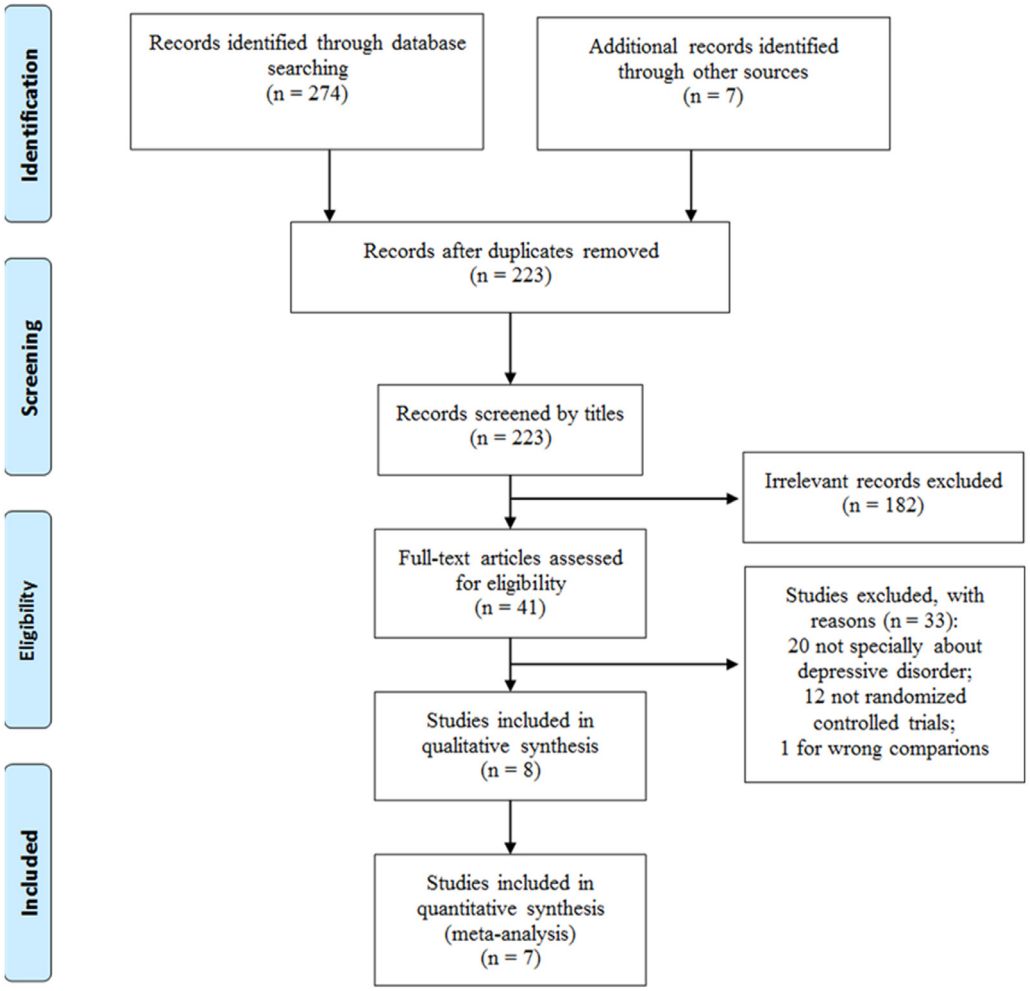

Fig. 1. The flow diagram of study search and selection.

2. Methods

This work was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and AMSTAR (Assessing the methodological quality of systematic reviews) guidelines. The protocol of this study had been registered on PROSPERO (CRD42019137287).

2.1. Literature search

Literature search was performed across PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), VIP and WANFANG DATA from January 1980 through May 2019 using the following phrases: ("Riluzole" OR "2-Amino-6-trifluoromethoxybenzothiazole" OR "Rilutek" OR "RP54274" OR "PK26124") AND ("Depressive Disorder" OR "Depressive Neuroses" OR "Endogenous Depression" OR "Depressive Syndrome" OR "Neurotic Depression" OR "Melancholia" OR "Unipolar Depressions"). No language or regional limitations were imposed. An additional search was performed for unpublished data using the ClinicalTrials.gov.

2.2. Study selection

All of the relevant literatures were reviewed by 2 reviewers (MQ-Y and RZ-Y), a third reviewer (HQ-W) helped achieve consensus. Inclusion criteria were (1) patients diagnosed as depressive disorder, (2) studies designed as RCTs that compared efficacy of riluzole versus placebo, (3) full texts or abstracts which could provide complete data. Studies were excluded if they met the following criteria: (1) non-RCTs or low quality RCTs, (2) studies not performed using human subjects, (3) letters, editorials, expert opinions, reviews, case reports, (4) duplicate publications, (5) studies not specifically concerning depressive disorder.

2.3. Data extraction and quality assessment

Data extraction and quality assessment were performed independently by 2 reviewers (RZ-Y, CX-W), the discrepancies between the two reviewers were resolved by their consensus or in consultation with the third reviewer (HQ-W).The following items were extracted from the involved studies: the author, year of publication, country, demographic characters, sample size, dose of riluzole, research periods, change in depression severity, the response rate, remission rate, adverse events, the relapse rate and time. The Primary outcome was change in depression severity, and the secondary outcomes were the response rate, remission rate, adverse events, the relapse time and rate. We also contacted corresponding authors to verify extracted data or request the missing data.

The quality of involved studies using the previously validated 7-point Jadad scale (Oremus et al., 2001). Studies scored 3 or less were considered as low quality. In addition, "the Cochrane Collaboration's tool for assessing risk of bias" was also used to assessed the methodological quality of RCTs (Higgins et al., 2011).

2.4. Statistical analysis

The meta-analysis was performed using the Stata 14.0 software (StataCorp, College Station, Texas) and Review Manager 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). For every individual study, Hedges' g was calculated for each outcome measure. In this approaches, it was possible to compare outcomes of change scores on different depression scales. To obtain this effect size, mean differences in change scores and standard deviations (SD) or pre-and post-means (+SD) were used. To avoid overestimation of the true effect sizes caused by the pre-post treatment correlation (Dunlap et al., 1996), change scores were preferred. When these values were not reported, we used exact F-, t- or p-values.

The heterogeneity was tested depending on the Cochran's Q test and I^2. $P < .05$ or $I^2 \geq 75\%$ is an indication of significant heterogeneity, a random-effects model was adopted; otherwise, a fixed effects model was used. We calculated SMD and 95% CI to analyze the continuous data, while for the dichotomous variables we calculated RR and 95% CI. Planned subgroup analyses were performed according to riluzole therapy (monotherapy or not). "Egger test" were used to assess the publication bias and sensitivity analysis was performed to assess the robustness and weigh the influence of each eligible study on the pooled outcomes.

3. Results

3.1. Literature search

The preliminary literature search yielded 281 potentially relevant records, finally 7 RCTs with a total of 373 patients were involved in our analysis (Salardini et al., 2016; Mathew et al., 2017; Ibrahim et al., 2012; Park et al., 2017; Mathew et al., 2010, 2015; Payne, 2017). The process of study search and selection is shown in Fig. 1.

3.2. Characteristics and risk of bias of included trials

The characteristics of the included studies are shown in Table 1. Among the 373 patients, 197 patients were allocated to the control group. In 4 studies the follow-up period was longer than 6 weeks (Mathew et al., 2017; Park et al., 2017; Salardini et al., 2016; Payne, 2017), in the 3 remaining studies the follow-up time were between 4 weeks and 5 weeks (Ibrahim et al., 2012; Mathew et al., 2010, 2015). All studies adopted 50 mg twice daily as the initial dose of riluzole, lactose or starch tablet, saline were used as placebo. According to the 7-point Jadad scale, 4 studies scored seven (Mathew et al., 2017; Salardini et al., 2016, 2010; Payne, 2017), 1 studies scored six (Mathew et al., 2015) and 2 studies got a five score (Park et al., 2017; Ibrahim et al., 2012).

The risk of bias assessed using "the Cochrane Collaboration's tool for assessing risk of bias" were shown in Fig. 2.

3.3. The primary outcomes: change in depression severity

Among the involved studies, 6 studies presented data related to change in depression severity as an outcome measure, they were reported as MADRS (Mathew et al., 2017; Ibrahim et al., 2012, 2010; Mathew et al., 2015; Payne, 2017) and HDRS (Salardini et al., 2016; Ibrahim et al., 2012;). In 3 studies patients were dosed with riluzole or placebo as monotherapy (Mathew et al., 2017, 2015; Payne, 2017), in 2 studies combination of riluzole and ketamine was dosed (Ibrahim et al., 2012; Mathew et al., 2010), combination of riluzole and citalopram was dosed in 1 study (Salardini et al., 2016). The subgroup analyses indicated that there was no significant difference between riluzole and placebo group when riluzole/placebo monotherapy ($P = .512$, $I^2 = 0\%$; SMD −0.078, 95% CI −0.335 to 0.178, $P = .549$) or combination of riluzole/placebo and ketamine ($P = .063$, $I^2 = 71\%$; SMD −0.427, 95% CI −0.968 to 0.115, $P = .122$) was dosed. While some difference was shown when combined riluzole with citalopram (SMD 0.844, 95% CI 0.315 to 1.374, $P = .002$) Fig. 3.

3.4. Response rate

Five studies reported response rate, which defined as at least a 50% reduction in MADRS or HDRS score (Salardini et al., 2016; Mathew et al., 2017; Ibrahim et al., 2012, 2015; Payne, 2017). The heterogeneity was not high ($P = .010$, $I^2 = 69.9\%$), the results of fixed effects model suggested that there was no significant difference between riluzole and placebo group (RR 1.201, 95% CI 0.908 to 1.587, $P = .199$) Fig. 4.

3.5. Remission rate

Three studies reported remission rate, defined as a HDRS score ≤ 7 or MADRS score ≤ 9 (Salardini et al., 2016; Mathew et al., 2017, 2015). The heterogeneity was low ($P = .841$, $I^2 = 0\%$) and pooled results indicated that there was no significant difference in remission rate between the two group (RR 2.026, 95% CI 0.932 to 4.406, $P = .075$) (Supplementary materials 1).

3.6. Relapse time and rate

Two studies reported relapse time and rate (Ibrahim et al., 2012; Mathew et al., 2010). The pooled results indicated that there was no difference in relapse rate (RR 0.971, 95% CI 0.632 to 1.492, $P = .893$) Fig. 5. The WMD of relapse time in riluzole group compared with placebo group was 5.245 days (95% CI 0.391 to 10.098, $P = .034$, Supplementary materials 2).

3.7. Adverse events

Six studies presented data related to adverse events, the three main symptoms were headache, fatigue and body pain (Salardini et al., 2016;

Table 1
Characteristics of included studies.

Study	Country	Study design	Total sample	Age	Administration method	Study period	Jadad score
Mathew et al. (2017)	America	RCTs	65	45.61 ± 12.45	Riluzole 50 mg twice daily vs Placebo	8 weeks	7
Park et al. (2017)	America	RCTs	19	49.22 ± 12.77	Riluzole 50 mg twice daily, increased on a weekly basis by 50 mg, maximum to 200 mg/day vs Placebo	8 weeks	5
Salardini et al. (2016)	Iran	RCTs	60	33.9 ± 7.21	Riluzole 50 mg+ citalopram vs Placebo+ citalopram	6 weeks	7
Ibrahim et al. (2012)	America	RCTs	42	47.2 ± 13.3	Riluzole 50 mg twice daily + ketamine vs Placebo + ketamine	4 weeks	5
Mathew et al. (2010)	America	RCTs	14	51.34 ± 11.48	Riluzole 100–200 mg/day+ ketamine vs Placebo+ ketamine	32 days	7
Mathew et al. (2015)	America	RCTs	79	47.55 ± 12.34	Riluzole 50 mg twice daily vs Placebo	4 weeks	6
Payne (2017)	America	RCTs	94	43.0 ± 10.46	50 mg twice daily, at four weeks increase to 100 mg twice daily vs Placebo	8 weeks	7

Abbreviations: RCTs, randomized controlled trials; vs, versus;.

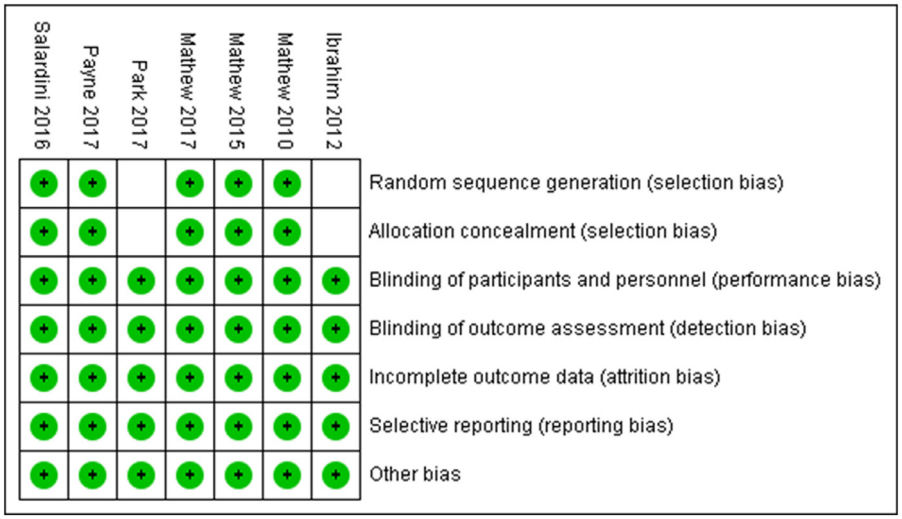

Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

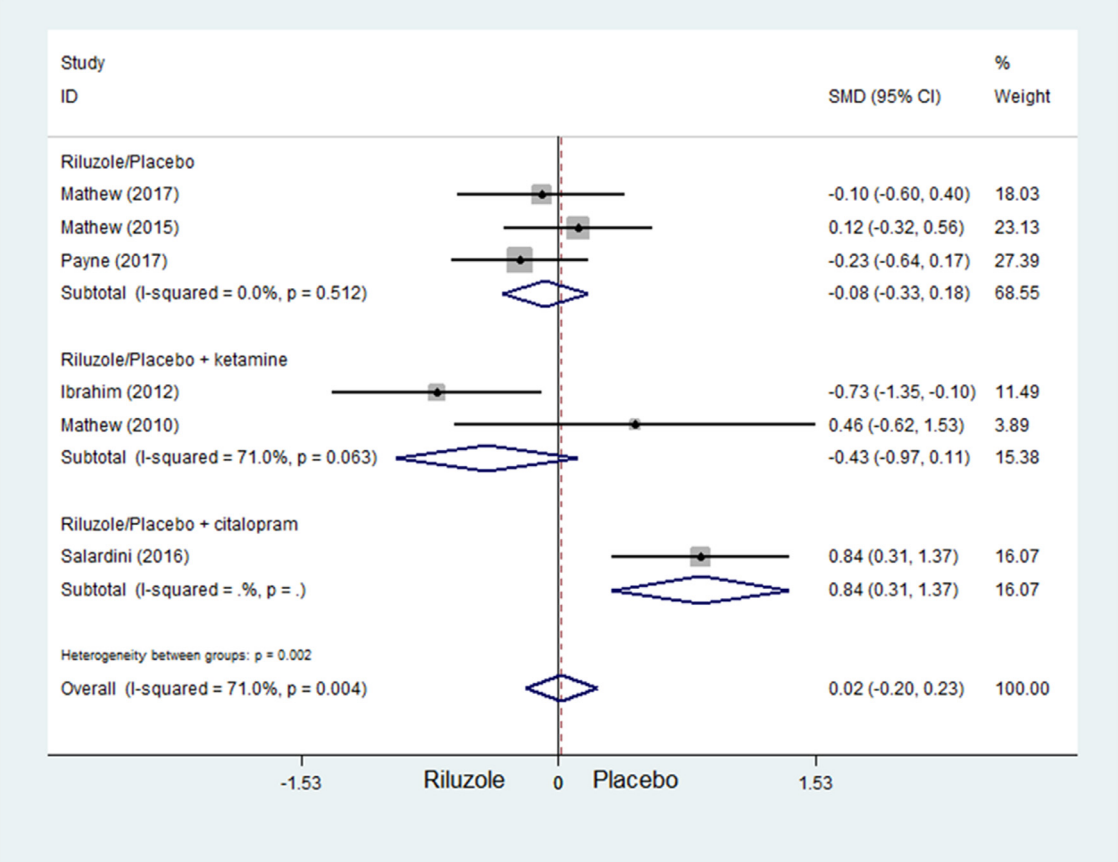

Fig. 3. The forest plot of subgroup analyses showing the comparison between riluzole and placebo for change in depression severity.

Mathew et al., 2017; Ibrahim et al., 2012; Park et al., 2017; Mathew et al., 2010; Payne, 2017). The results of fixed effects model (P = .905, I^2 = 0%) indicated that the difference between riluzole and placebo group was not significant (RR 1.296, 95% CI 0.920 to 1.824, P = .138, Supplementary materials 3).

3.8. The publication bias and sensitivity analysis

The egger test of change in depression severity was performed (P = .803), indicated that the risk of publication bias was low. Sensitivity analysis was performed by removing each individual study from the model, and there was no evidence that removal of any single study resulted in a change in the conclusion that riluzole did not show any efficacy in change of depression severity (Supplementary materials 4).

4. Discussion

This analysis identified 373 patients derived from 7 randomized placebo-controlled trials and found that riluzole did not show

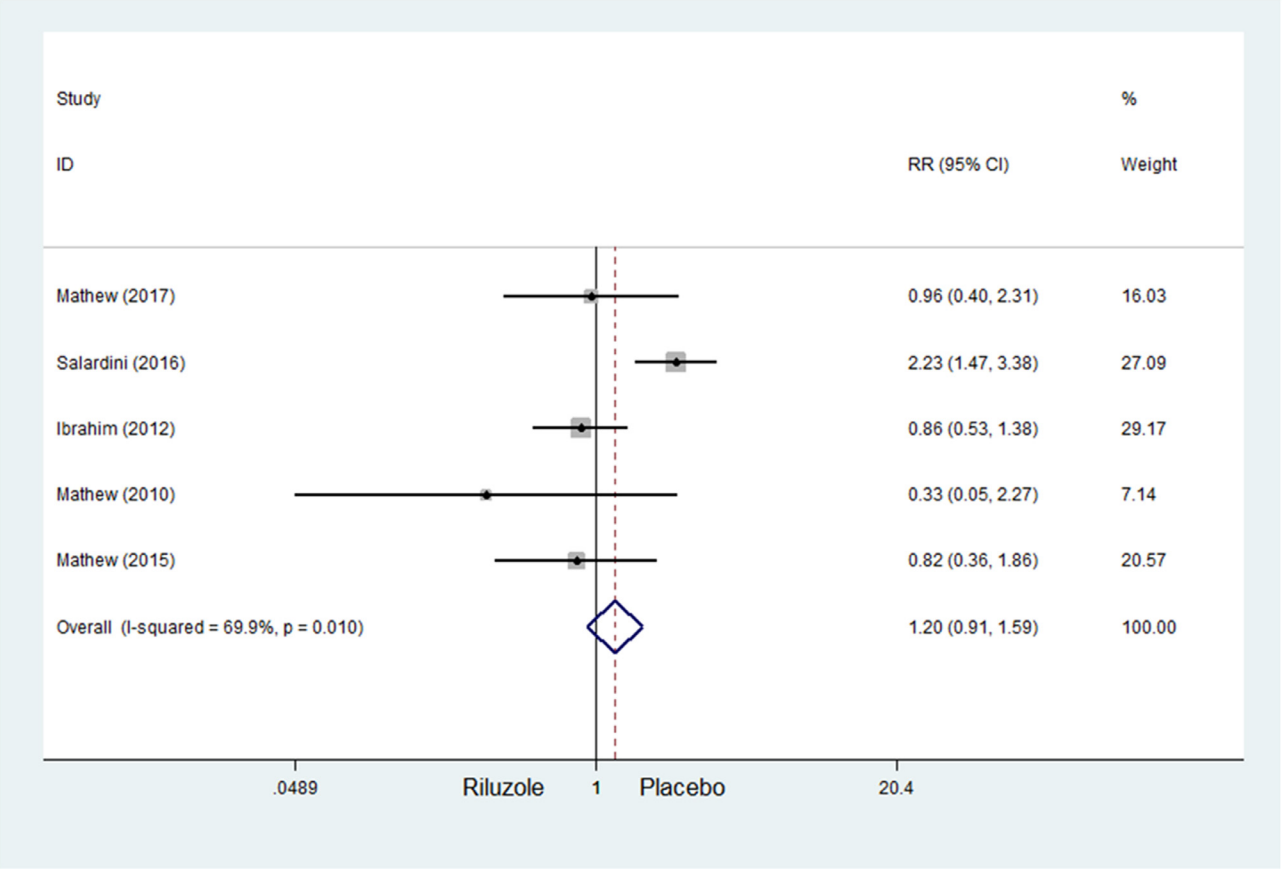

Fig. 4. The forest plot showing the comparison between riluzole and placebo for response rate.

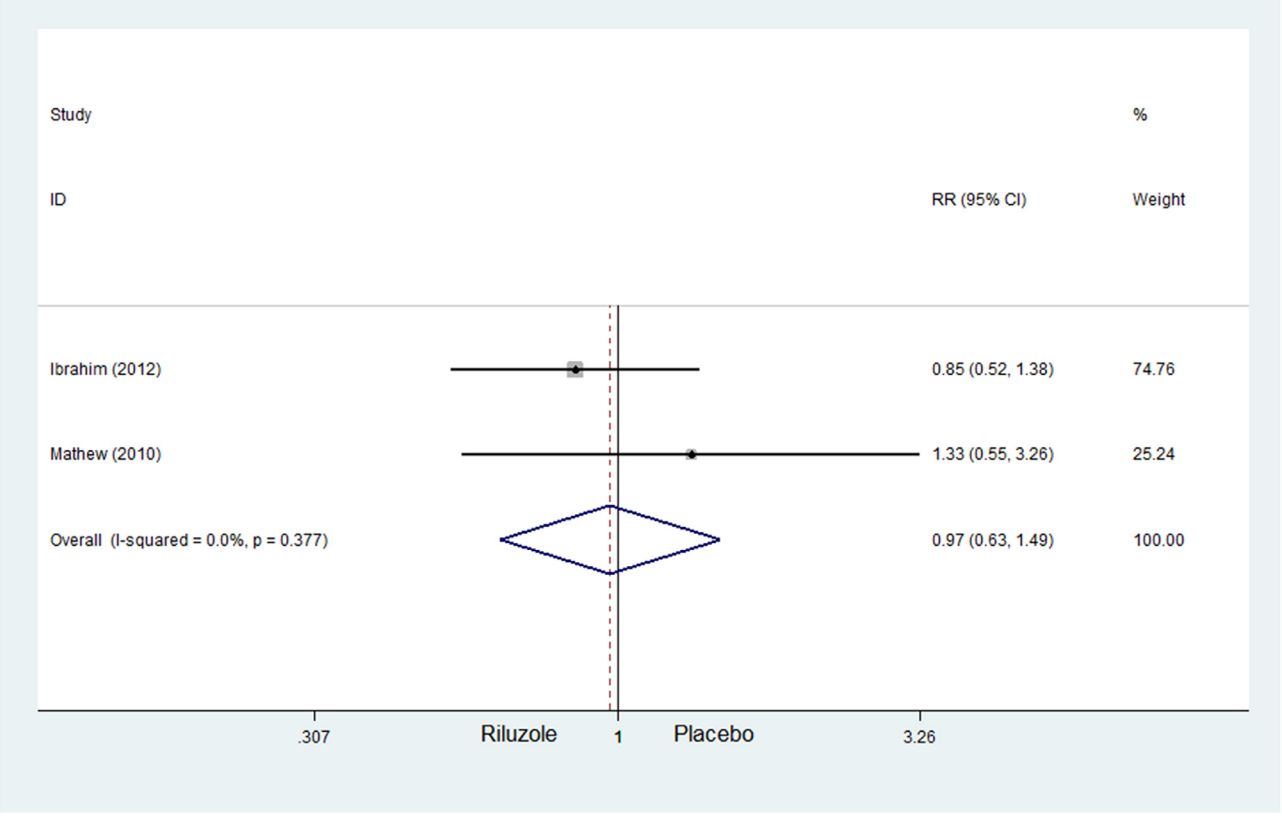

Fig. 5. The forest plot showing the comparison between riluzole and placebo for relapse rate.

antidepressant effects compared to placebo. Our findings are in consistent with Caddy et al. who reported that riluzole proved to have no more benefits for depression than placebo (Caddy et al., 2015).

Our results contradict several non-controlled studies, which reported riluzole could augment antidepressant and anxiolytic effects (Sanacora et al., 2007; Banasr et al., 2010), furthermore, antidepressant effects of riluzole were also shown in depression animal models (Gourley et al., 2012). These discrepancies may result from several reasons: First, the dose of riluzole used was different. Dose-dependent effects of riluzole were found for the expression of BDNF and GLT1 (Pereira et al., 2017), and antidepressant effects were shown in an open-label trial for bipolar depression performed with the dose of 171.4 mg daily (Banasr et al., 2010), while the mean daily dose of 100 mg was used in most studies involved in our analysis. Therefore, higher doses of riluzole may result in more pronounced effects.

Second, the depression severity and duration of patients might be different between studies. Kinon et al. reported that the efficacy of glutamate-based pharmacotherapies may vary as a function of illness duration or medication history (Ates et al., 2013).

Third, the trial duration strategies were different, antidepressant effects of riluzole had shown time-dependent. In a 6-week study significantly greater improvement and response were observed in riluzole group than the placebo group (Duncan et al., 2013), while differences were not observed in a 4-week study (Mathew et al., 2017). Furthermore, a longer term treatment last for 17 weeks, reported riluzole improved memory performance in aged rats (Du et al., 2007).

Fourth, combination drug might affect the antidepressant effects of riluzole. Salardini et al. gave a combination therapy consisted of riluzole and citalopram to depressive disorder patients, significant efficacy was observed in the riluzole group (Ates et al., 2013). A previous open-label study found that riluzole, administered in conjunction with lithium, had antidepressant properties (Banasr et al., 2010). Ibrahim et al. reported that riluzole did not show adjunctive antidepressant efficacy compared to placebo following ketamine, and surmised that riluzole might not maintain the neurobiological changes necessary for capturing and sustaining the antidepressant effects of ketamine (Ibrahim et al., 2012). Therefore, the timing of riluzole dosing related to combination drugs administration is also very important in achieving a sustained antidepressant effect.

Although the mechanism of riluzole for mood disorder is not fully understood, despite its use in amyotrophic lateral sclerosis and neurodegenerative disorders for over 20 years (Du et al., 2007). The main explanations of mechanisms modulating glutamatergic system by riluzole is proposed to increase glutamate metabolism and transportation, enhance glutamate uptake by either synaptic neurons or astrocytes, stimulate the expression of excitatory amino acid transporter 2 (EAAT2), enhance brain-derived neurotrophic factor signaling. In addition, riluzole enhanced expression of the neuronal metabolite N-acetyl-aspartate (NAA) in hippocampus in patients suffered from generalized anxiety disorder.

No significant difference was identified between the riluzole group and placebo group in terms of relapse rate, but the pooled results suggested that the relapse time of riluzole group was 5 days longer than placebo group. This may be of great significance in clinic. The adverse events reported in clinical studies were headache, fatigue, body pain, suicide attempts, liver transaminases and neutropenia, the pooled results showed a favorable safety of riluzole in patients with DD.

To the best of our knowledge, this is the first meta-analysis of riluzole used for DD. Another notable strength of this study is that all included studies are randomized placebo-controlled trials and the whole procedure was performed according to PRISMA criteria to ensure the transparency and replicability of the results.

Nonetheless, some limitations exist in our study. First of all, the quantity of included studies is not large, and the sample of individual studies is small. Additionally, moderate heterogeneity is existent in individual effect size, which could be explained by the different methods of define criterion.

5. Conclusion

In conclusion, our work showed that riluzole did not have antidepressant efficacy compared to placebo in monotherapy or riluzole-ketamine combined therapy, while it might relieve depression severity to some extent when combined with citalopram. Riluzole showed favorable safety for DD. Furthermore, the longer relapse time of riluzole group might have clinical significance to some extent, although this had no statistical difference. More well designed RCTs will help clarify the potential association between riluzole and DD.

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CRediT authorship contribution statement

Ruzhan Yao: Conceptualization, Validation, Investigation, Writing - review & editing. **Haiquan Wang:** Conceptualization, Data curation, Writing - original draft, Writing - review & editing. **Mingqi Yuan:** Conceptualization, Data curation, Writing - original draft, Writing - review & editing. **Guanglin Wang:** Conceptualization, Validation, Investigation, Writing - review & editing. **Chengxi Wu:** Conceptualization, Data curation, Writing - review & editing.

Declaration of Competing Interest

The authors have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2020.112750.

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