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Review article

# Efficacy and tolerability of riluzole in psychiatric disorders: A systematic review and preliminary meta-analysis

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ABSTRACT

There is a pressing need for better pharmacological treatment strategies for psychiatric disorders as current treatment often results in partial symptom remission and unwanted side effects. A point of entry may be the glutamatergic system since glutamatergic dysregulation contributes to multiple psychiatric disorders. We evaluated the evidence from randomized controlled trials (RCTs) regarding the use of the glutamatergic drug riluzole in mental illnesses; and conducted preliminary meta-analyses of its effectiveness in treating obsessive-compulsive disorder (OCD) and depression.

A systematic search was performed using PubMed (Medline), Embase, Cochrane Database of Systematic Reviews and PsycINFO. Meta-analyses were performed using Comprehensive Meta-Analysis software.

Twenty-three RCTs were included for qualitative analysis and showed positive effects of adjunctive/monotherapy riluzole in patients with OCD, depression, autism, substance abuse and schizophrenia. Seven studies were also used for quantitative analysis, which revealed positive but non-significant effects on OCD and depression. Riluzole was generally well tolerated with few serious adverse events.

The studies included in this systematic review were highly heterogeneous and the number of studies was limited per diagnostic condition. Moreover, few studies have examined riluzole as a single treatment. We suggest carrying out further work to provide definitive evidence for the benefit of riluzole in psychiatric illness.

## 1. Introduction

Riluzole is an antiglutamatergic agent that is approved for the treatment of amyotrophic lateral sclerosis (ALS) (Miller et al., 2012). Chemically, riluzole is a benzothiazole that has antiepileptic (Benavides et al., 1985) and neuroprotective properties and a favorable side effect profile (Liboux et al., 1999). Riluzole primarily modulates the glutamatergic system, a system that is increasingly linked with the pathology of mood, anxiety and psychotic disorders. Riluzole is assumed to act by inhibiting voltage-gated sodium channels, thereby reducing neurotransmitter release, and to enhance astrocytic uptake of extracellular glutamate (Pittenger et al., 2008). In vitro, these effects are mediated by processes linked to the n-methyl-D-aspartate (NMDA) receptor (Doble, 1996). Additionally, riluzole interacts with inhibitory neurotransmitters, increasing the depolarizing effect of GABA and thereby enhancing GABAergic inhibitory function (He et al., 2002; Mohammadi et al., 2001). Riluzole may exert its glutamate inhibiting effects also by increasing glutamate reuptake via glia cells (dos Santos Frizzo et al., 2004). In vitro, riluzole is also shown to attenuate release of acetylcholine and dopamine (Jahn et al., 2008; Jehle et al., 2000). These effects may be achieved at low riluzole concentrations (Urbani and Belluzzi, 2000). Riluzole is thus thought to reduce neuronal excitability and possibly increase neuroprotection through several mechanisms. Previous systematic reviews have assessed the pharmacological effects of riluzole and revealed promising initial trials in psychiatric disorders. At that time however, randomized controlled trials were lacking (Grant et al., 2010; Pittenger et al., 2008; Zarate Jr and Manji, 2008). Here, we provide an updated and comprehensive systematic review investigating the efficacy and tolerability of riluzole in the treatment of psychiatric disorders. In addition, we quantitatively examine its effects on depressive and obsessive-compulsive symptoms.

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**Table 1**
Main characteristics and results of studies.

| Reference | Diagnosis | N | % female | Age in years (M ± SD) | Concomitant therapy | Riluzole dose (total/day)[a] | Primary outcome measures | Treatment duration (weeks) | Outcome with effect sizes |
|---|---|---|---|---|---|---|---|---|---|
| **Obsessive-compulsive disorders** | | | | | | | | | |
| Emamzadehfard et al. (2016) | OCD | 54 | 70% | 18–60 (34.86 ± 10.25) | Fluvoxamine week 1–4 100 mg/d; week 5–10 200 mg/d | 100 mg/d | Y-BOCS total, obsession, compulsion scores | 10 | Greater reduction Y-BOCS total ($p = .04$; Cohen's $d = 0.59$) and compulsion subscale ($p = .03$; Cohen's $d = 0.64$); no effect on obsession subscale ($p = .11$; Cohen's $d = 0.44$). |
| Grant et al. (2014) and Joseph et al. (2011)[g] | OCD + ASD | 60 | 27% | 7–17 (14.47 ± 2.35) | Mostly SSRI stable last 2 months | 100 mg/d[b] | CY-BOCS, CGI-S,CGI-I, CGAS scores | 12 | No effect on CY-BOCS total ($p = .84$; Cohen's $d = -0.44$) and subscales, CGI ($p = .98$; Cohen's $d = -0.49$) and CGAS ($p = .38$; Cohen's $d = -0.66$). |
| Lemmon et al. (2015) | Tourette syndrome | 15 | 0% | 8–17 (12.9) | – | 200 mg/d[b] | YGTSS total, TTS-subscale score | 6 | No effect on TTS ($p = .85$) and YGTSS ($p = .35$). No effect on CY-BOCS ($p = .71$) and MACS ($p = .4$) |
| Pittenger et al. (2015) | OCD | 38 | 46% | (39.02 ± 3.15) | Placebo pre-treatment 2 weeks; followed by stable dose SSRI/clomipramine | 100 mg/d | Y-BOCS total score | 12 | No effect on Y-BOCS total ($p = .48$) and subscales. No significant effect on HAM-A and HAM-D. |
| **Depressive disorders** | | | | | | | | | |
| Ibrahim et al. (2012)[c] | MDD | 42 | 38% | 18–65 (47.2 ± 13.2) | Pre-treatment with ketamine infusion 0.5 mg/kg in 40 min | 200 mg/d[b] | MADRS score | 4 | No effect on MADRS ($p = .23$). 62% reached response criteria between ketamine-infusion and start treatment; No effect on HAM-D ($p = .81$), BDI ($p = .35$), VAS-D ($p = .53$), HAM-A ($p = .88$). |
| Mathew et al. (2010) | MDD | 14 | 39% | 21–70 (48.2 ± 11.8) | Pretreated with lamotrigine or placebo 2 h prior to Ketamine infusion 0.5 mg/kg in 40 min | 200 mg/d[b] | Time to relapse | 4.5 | Riluzole did not protect against post-ketamine relapse in the first month. No significant difference in time-to-relapse ($p = .68$) and MADRS-score at exit ($p = .62$). |
| Mathew et al. (2015, 2017)* | MDD | 104[d] | 56% | 18–65 (46.2 ± 12.4) | Sertraline 50–150 mg/d or SSRI/SNRI/Bupropion | 100 mg/d | MADRS score | 8 | No effect on MADRS ($p = .10$). No effect on response ($p = .83$) and remission ($p = .98$) rates. |
| Niciu et al. (2014)[c] | MDD | 32 | 38% | 18–65 (46.5 ± 13.7) | Pre-treatment ketamine infusion 0.5 mg/kg in 40 min | 100–200 mg/d | MADRS score | 4 | No effect on MADRS in ketamine non-responders ($p = .44$). |
| Park et al. (2017) | BD | 19 | 32% | 18–70 (46.63 ± 12.94) | – | 200 mg/d[b] | MADRS score | 8 | No effect on MADRS ($p = .09$). Improvement on HAM-A ($p = .046$); No effect on HAM-D ($p = .12$) and YMRS ($p = .17$). |
| Salardini et al. (2016) | MDD | 60 | 32% | 18–50 (33.90 ± 7.24) | Citalopram week 1 20 mg/d; week 2–6 40 mg/d | 100 mg/d | HAM-D score every 2 weeks; | 6 | Significantly more improvement on HAM-D from baseline to week 2 (Cohen's $d = 1.06$), 4 (Cohen's $d = 0.90$) and 6 |

(*continued on next page*)

**Table 1** (*continued*)

| Reference | Diagnosis | N | % female | Age in years (M ± SD) | Concomitant therapy | Riluzole dose (total/day)[a] | Primary outcome measures | Treatment duration (weeks) | Outcome with effect sizes |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | (Cohen's $d = 0.87$). More early improvers ($p < .001$). |
| Wilkinson et al. (2016, 2018)* | MDD | 104[d] | 52% | 18–65 (46.1 ± 12.2) | SSRI/ SNRI/ bupropion | 100 mg/d | Correlation pBDNF-sBDNF and response rate | 8 | No correlation serum ($p = .23$) or plasma ($p = .25$) BDNF and depressive improvement. Responders had lower pre-treatment sBDNF and pBDNF compared to non-responders. |
| **Autism spectrum disorders** | | | | | | | | | |
| Ghaleiha et al. (2013) | ASD | 49 | 18% | 5–12 (8.0 ± 2.0) | Risperidone 2 mg/d for children 10–40 kg and 3 mg/d for 40 + kg | 100 mg/d[b] | ABC irritability | 10 | Greater reduction ABC- irritability subscale ($p < .001$; Cohen's $d = 0.70$) and lethargy (Cohen's $d = 0.76$), stereotypic behavior (Cohen's $d = 0.67$) and hyperactivity subscales (Cohen's $d = 0.94$). No significant effect on speech subscale. |
| Nicolson et al. (2017) | ASD | 58 | N.R. | (11.4 ± 3.0) | N.R. | 100mg[b] | YBOCS, RBS, ABC | 12 | No significant differences on social withdrawal, repetitive, or ritualistic behaviour (ABC-SW: $p = .3$; YBOCS: $p = .1$; RBS: $p = .1$). Significantly greater reduction in scores on the ABC-Irritability ($p = .03$) and ABC—Hyperactivity ($p = .03$) subscales in riluzole group. |
| Wink et al. (2018)[e] | ASD | 8 | 14% | 12–25 (16.02 ± 1.9) | At least one antipsychotic drug | 200 mg/d[b] | CGI-I and ABC-irritability | 5 | No effect on CGI ($p = .66$) and ABC-I ($p = .64$). |
| **Substance disorders** | | | | | | | | | |
| Ciraulo et al. (2005) | Cocaine dependence | 33 | 24% | 18–59 (41.4 ± 6.95) | Cognitive behavioral counseling | 100 mg/d | Urine analyses; self-reported use and CGI scores | 8 | No effect on urine analysis in week 1–4 ($p = .98$) and week 5–8 ($p = .6$); No significance in self-reported use and CGI-scores. |
| Farahzadi et al. (2018) | Methamphetamine dependence | 86 | 0% | 18–65 (36.76 ± 7.94) | – | 100 mg/d | Weekly visits; Urine test results | 12 | More weekly visits ($p = .043$) and lower positive urine-tests ($p = .004$). Significant more improvement on ASSA (Cohen's $d = 3.65$), AWQ (Cohen's $d = 2.37$) VAS-C (Cohen's $d = 2.05$), STCQ (Cohen's $d = 1.44$), HAM-D (Cohen's $d = 1.10$). |
| **Schizophrenia** | | | | | | | | | |
| Farokhnia et al. (2014) | Schizophrenia | 50 | 14% | 18–50 (32.92 ± 7.42) | Risperidone flexible dose 2–6 mg/d | 100 mg/d[b] | PANSS total and subscale score | 8 | Significant improvement on PANSS total (Cohen's $d = 1.37$) negative subscale (Cohen's $d = 1.28$), and psychopathology subscale (Cohen's $d = 1.04$). No significance on positive subscale (Cohen's $d = 0.36$) and HAM-D (Cohen's $d = -0.09$). |
| **Single dose challenge studies** | | | | | | | | | |
| Ajram et al. (2015) | ASD | N.R. | | N.R. | – | 50mg | | Single dose | |

(*continued on next page*)

**Table 1** (*continued*)

| Reference | Diagnosis | N | % female | Age in years (M ± SD) | Concomitant therapy | Riluzole dose (total/day)[a] | Primary outcome measures | Treatment duration (weeks) | Outcome with effect sizes |
|---|---|---|---|---|---|---|---|---|---|
| Vingerhoets et al. (2018) | 22q11 DS | 32 | | (32.5) | – | 50mg | Inhibitory index in left basal ganglia and bilateral prefrontal cortex<br>GABA + GLU levels in ACC and striatum[f] and correlation CANTEB | Single dose | In basal ganglia riluzole increased inhibitory in both groups, but in prefrontal cortex only inhibitory index change in ASD-group ($p$ = .038).<br>Correlations between verbal memory-ACC GLU (negative; $p$ = .030); glutamate reactivity (negative; $p$ = .010); attention-ACC GLU (negative; $p$ = .016); attention-GLU/GABA ratio (negative; $p$ = .050); attention-ACC GABA (positive; $p$ = .024); attention-GLU/GABA ratio (negative; $p$ = .047); visual memory-striatal GLU-levels (positive; $p$ = .043). |
| Zarate (2011) | MDD | N.R. | | N.R. | Single dose infusion ketamine | N.R. | Slow wave parameters on EEG and mood measurement | Single dose | Mood effects at 230 min correlated with effect on high amplitude slow waves ($p$ < .05) and significant increase of number high amplitude waves during first NREM sleep. |

n: sample size, M: mean, SD: standard deviation, N.R.: not reported, ASD: autism spectrum disorder, MDD: major depressive disorder, OCD: obsessive compulsive disorder, yr: years, Y-BOCS: Yale-Brown Obsessive Compulsive Scale, HAM-D: Hamilton depression rating scale, CGAS: children global assessment score, HAM-A: Hamilton anxiety scale, MADRS: Montgomery-Asberg Depression Rating Scale, PANSS: positive and negative syndrome scale, CGI: clinical global impression, BDI: Beck's depression index, RBS: Repetitive Behavior Scale, VAS: visual analogue scale, YMRS: Young mania rating scale, ABC: activities-specific balance confidence scale, ASSA: Amphetamine Selective Severity AWQ: Assessment Amphetamine Withdrawal Questionnaire, STCQ: Stimulant Craving Questionnaire, NREM: non-rapid eye movement.

[a] Riluzole twice daily given.

[b] Increased from lower starting dose.

[c] Niciu (2014) used partially same participants as Ibrahim (2012) but analyzed only ketamine non-responders.

[d] Used same participants but examined different primary outcome measures.

[e] Each participant received 5 weeks riluzole and 5 weeks 5 placebo separated by 2 weeks wash-out.

[f] ACC-Anterior Cingular Cortex; measured with 7 Tesla Magnetic Resonance Imaging.

[g] The papers by Joseph et al. (2011), Grant et al. (2014), Mathew et al. (2015), Mathew et al. (2017), Wilkinson et al. (2016) and Wilkinson et al. (2018) are reported as one sample in this table, since they report on the same subjects and thus main characteristics are the same.

## 2. Methods

### 2.1. Literature search

This review was performed according to the Preferred Reporting for Systematic Reviews and Meta-analysis (PRISMA) Statement (Moher et al., 2015). The literature search was conducted by two independent researchers (J.B. & M.H.) using PubMed (Medline), Embase, Cochrane Database of Systematic Reviews, and PsychINFO. Combinations of the following search terms were used: “riluzole”, “Rilutek” and “psychiatric”, “mental disorder”. The search had no year and language restrictions. See Supplementary Table 1 (Table S1) for an example search string. The search cut-off date was February 19th, 2019. Reference lists of the included studies were searched for cross-references. After independent screening was performed by J.B. and M.H., consensus about the included studies was reached between J.B., M.H. and J.Z.

### 2.2. Inclusion criteria

Articles were included when the following inclusion criteria were met: 1) randomized, double-blind placebo-controlled trials that assessed the effect of riluzole; 2) the included patients were diagnosed with a psychiatric disorder, according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR, DSM-5) (Association, 2013; Frances, 1994), or the International Classification of Diseases (ICD-9 or ICD-10); 3) studies were published in a peer-reviewed journal or conference book. Risk of bias was assessed independently by J.B. and M.P. using the Cochrane Risk of Bias tool for randomized controlled trials (Table S2) (Higgins et al., 2011).

### 2.3. Outcome measures

#### 2.3.1. Qualitative synthesis

The efficacy of riluzole compared to placebo on symptoms of a psychiatric disorders were regarded the primary outcome measure. Additionally, adverse effects of the included studies are reported.

#### 2.3.2. Quantitative synthesis

The primary outcome measures were depressive symptoms in patients with major depressive disorder (MDD) and obsessive-compulsive symptoms in patients with obsessive-compulsive disorder (OCD). Depressive symptoms were measured with the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) or the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1986). In case multiple rating scales were used, preference was given to the MADRS or HAM-D. Obsessive-compulsive symptoms were measured with the (Children's) Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989a, 1989b; Scahill et al., 1997), of which total and subscale scores were used.

### 2.4. Statistics

Comprehensive Meta-Analysis (CMA) software version 2.0 was used to perform all analyses, using a random-effects model (Borenstein et al., 2005). For every individual study, Hedges’ *g* was calculated for each outcome measure. To obtain this effect size, per treatment arm, mean differences in change scores (end of treatment minus baseline) 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. All effect sizes were calculated twice independently from the original articles to check for errors.

Studies were combined in meta-analyses to calculate a mean weighted effect size for each outcome measure, using a random-effects model. To investigate whether studies could be taken together to share a common population effect size, the Q-value and $I^2$-statistic were evaluated for each analysis. The Q-statistic tests the existence of heterogeneity, and displays a chi-square distribution with k-1 degrees of freedom (k = number of studies), where Q-values higher than the degrees of freedom indicate significant between-studies variability. $I^2$ reflects which proportion of the observed variance reflects differences in true effect sizes, rather than sampling error, ranging from 0 to 100%. Values of 25%, 50%, and 75% can be interpreted as low, moderate, and high, respectively (Higgins et al., 2003).

Additionally, funnel plots were inspected for asymmetry in order to check for publication bias. Potential asymmetry was tested with Egger's test, using a significance level of $\alpha = 0.05$ (2-tailed). Effect sizes with a p-value smaller than 0.05 were considered statistically significant. Effect sizes were interpreted according to the guidelines by Cohen, with an effect size of 0.20 indicating a small effect, 0.50 a medium and over 0.80 a large effect (Cohen, 1988).

## 3. Results

A flow diagram of the literature search is depicted Fig. 1. After screening on title and abstract, the search yielded 24 articles. After full-text reading 23 articles, describing 20 trials on riluzole use in psychiatric disorders remained, which are described in Table 1 (Ajram et al., 2015; Ciraulo et al., 2005; Emamzadehfard et al., 2016; Farahzadi et al., 2018; Farokhnia et al., 2014; Ghaleiha et al., 2013; Grant et al., 2014; Ibrahim et al., 2012; Joseph et al., 2011; Lemmon et al., 2015; Mathew et al., 2015, 2017, 2010; Niciu et al., 2014; Nicolson et al., 2017; Park et al., 2017; Pittenger et al., 2015; Salardini et al., 2016; Vingerhoets et al., 2018; Wilkinson et al., 2018, 2016; Wink et al., 2018; Zarate, 2011). Seven studies were included in the meta-analyses (see Table 2 for descriptive information). One study used a cross-over design, only the outcomes of the first six weeks were included in the analyses (Mathew et al., 2017). Taken these studies together, the efficacy of riluzole versus placebo was quantitatively assessed in a total of 451 patients.

### 3.1. Qualitative synthesis

#### 3.1.1. Depressive disorders

Eight studies investigated riluzole in patients with depressive disorders, including MDD and bipolar depression (BD) (Ibrahim et al., 2012; Mathew et al., 2015, 2017, 2010; Niciu et al., 2014; Park et al., 2017; Salardini et al., 2016; Wilkinson et al., 2018, 2016). One study, described in two articles, focused on Brain Derived Neurotrophic Factor in plasma (pBDNF) and serum (sBDNF) and reported lower pBDNF and sBDNF levels at baseline in responders to riluzole (Wilkinson et al., 2018, 2016). The remaining six trials investigated reduction of depressive symptoms as primary outcome, measured by MADRS and HAM-D scores. Three of these studies used a design investigating post-ketamine relapse and potential effects of riluzole on relapse prevention after ketamine infusion or ketamine non-responders (Ibrahim et al., 2012; Mathew et al., 2010; Niciu et al., 2014). One study investigated efficacy of riluzole as monotherapy for depression (Park et al., 2017). The efficacy of riluzole on depressive symptoms is also included in the quantitative assessment.

#### 3.1.2. Obsessive-compulsive disorders

Of the included articles, five publications analyzed disorders related with obsessive-compulsive behavior (Emamzadehfard et al., 2016; Grant et al., 2014; Joseph et al., 2011; Lemmon et al., 2015; Pittenger et al., 2015) summarized as OCD. One small trial was done in children with Tourette Syndrome and examined the effect of riluzole on tics (Lemmon et al., 2015). Riluzole showed no superior effect compared to placebo in reducing tic-related behavior. Efficacy of riluzole on

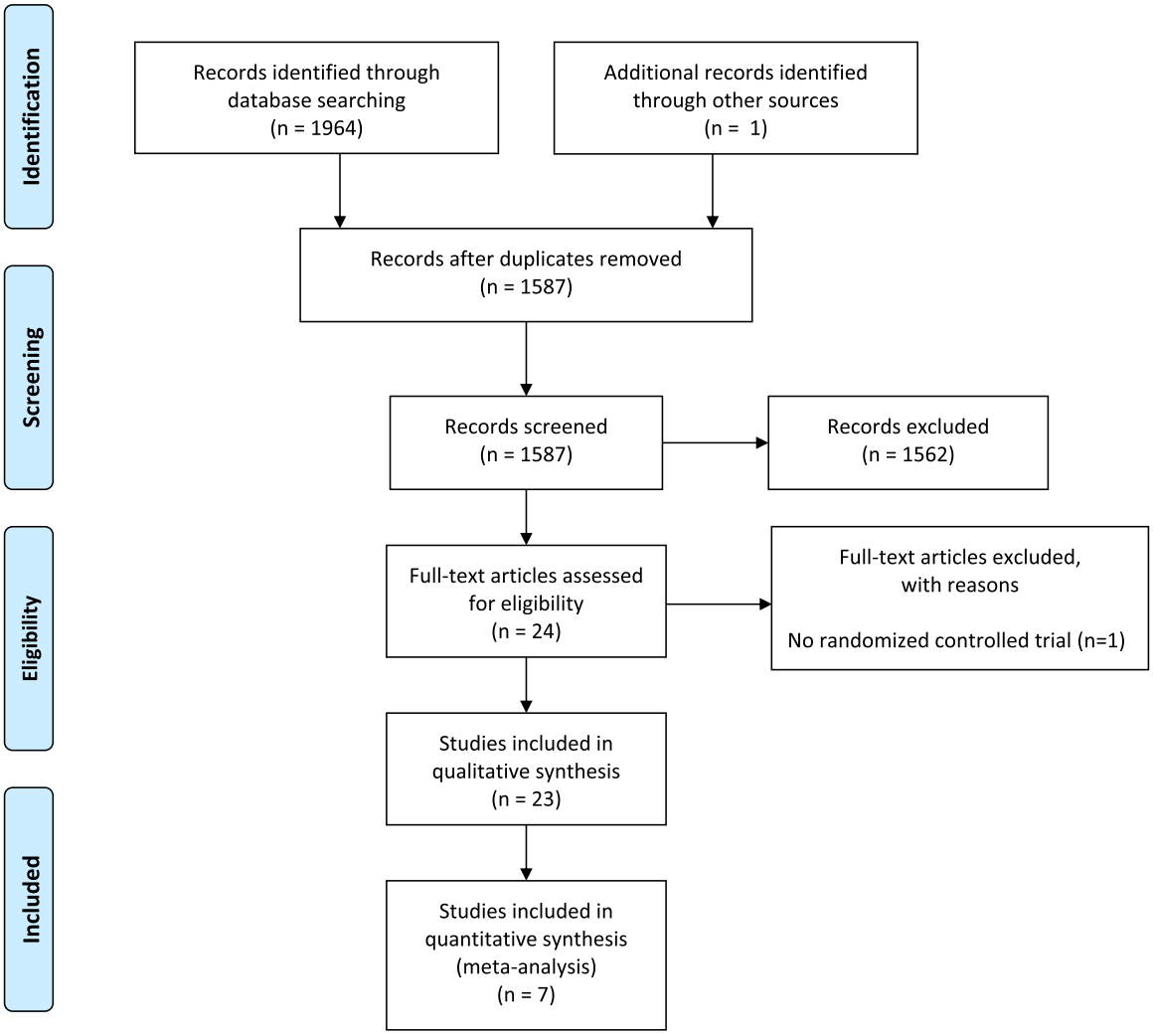


**Fig. 1.** Flow diagram of the search.

obsessive-compulsive symptoms is also summarized in the quantitative analyses.

### 3.1.3. Autism spectrum disorders

Three studies examined efficacy of riluzole in autism spectrum disorders (ASD) (Ghaleiha et al., 2013; Nicolson et al., 2017; Wink et al., 2018). Long-term adjunct treatment (10–12 weeks) in young children with ASD resulted in a significant effect on irritability (Ghaleiha et al., 2013) and long-term monotherapy resulted in reduction of irritability and hyperactivity (Nicolson et al., 2017). However, in another sample of children and young adults (age 12–25 years), no such effect of adjunctive riluzole was found (Wink et al., 2018).

### 3.1.4. Other psychiatric disorders including psychosis spectrum disorders

Two studies investigated the efficacy of riluzole in treatment on symptoms related to substance abuse (Ciraulo et al., 2005; Farahzadi et al., 2018). Methamphetamine dependent patients responded positively on riluzole monotherapy with respect to severity of dependence, withdrawal, craving and depressive symptoms (Farahzadi et al., 2018), while in cocaine dependent patients no effect was found when riluzole was given in combination with cognitive behavioral therapy (Ciraulo et al., 2005). The only randomized controlled trial to date with riluzole in schizophrenia (Farokhnia et al., 2014) investigated effects of riluzole augmentation of risperidone on positive and negative symptoms in patients with schizophrenia and reported significant positive effects of riluzole on negative symptoms after 12 weeks of treatment.

### 3.1.5. Single dose challenge studies

A single dose study in patients with 22q11-Deletion Syndrome (22q11DS) found higher baseline glutamate levels in 22q11DS patients

**Table 2**
Statistical results regarding all outcome measures.

| Outcome | Studies (k) | Subjects (n) | Hedges' *g* (95% CI) | *p*-value | $I^2$ (%) | Q-value (*p*-value) | Egger's test (*p*-value) |
|---|---|---|---|---|---|---|---|
| Depressive symptoms | 4 | 204 | .090 (−0.547 - 0.727) | .78 | 76.68 | 12.87 (0.005) | .86 |
| Obsessive-Compulsive symptoms | | | | | | | |
| Y-BOCS total | 3 | 138 | .130 (−0.260 - 0.520) | .51 | 31.43 | 2.12 (0.233) | .88 |
| Y-BOCS compulsion | 3 | 138 | .73 (−0.158 - 0.504) | .31 | 0 | 1.84 (0.398) | .99 |
| Y-BOCS obsession | 3 | 138 | .138 (−0.354 - 0.630) | .58 | 54.05 | 4.35 (0.113) | .82 |

k: number of studies, n: sample size, Y-BOCS: Yale-Brown Obsessive Compulsive Scale, CI: confidence interval.

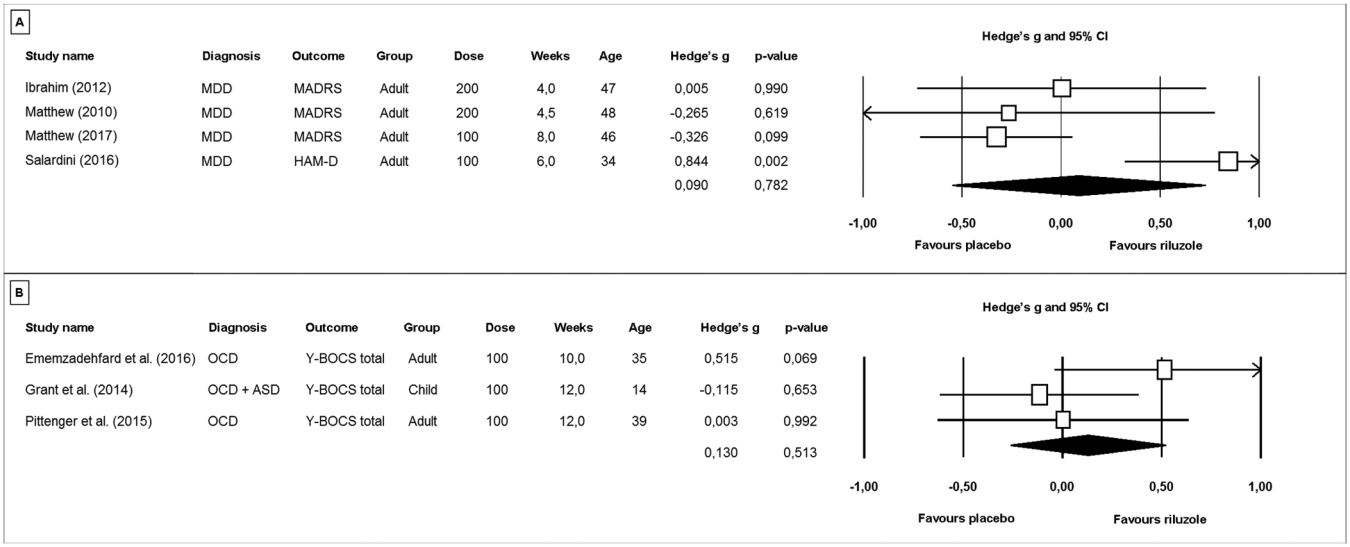


**Fig. 2.** Meta-analysis of the effect of riluzole on depressive symptom severity (A) and obsessive-compulsive symptom severity (B).

compared to controls and a decrease in glutamate concentrations after riluzole challenge (Vingerhoets et al., 2018). In MDD one study provided a single dose of riluzole and found that the mood effects after 230 min correlated with slow wave parameters on electroencephalogram (Zarate, 2011). In ASD, one single-dose study investigated effects on measures of glutamate and GABA in the brain using MR-spectroscopy (Ajram et al., 2015). Riluzole increased the relative proportion of GABA in the prefrontal cortex of the ASD group but not in the control group. In addition, exposure to a single dose of riluzole did not alter the functional connectivity of the prefrontal lobe in controls but 'restored' functional connectivity in the ASD group to a level comparable with the control baseline (Ajram et al., 2015).

### 3.2. Quantitative synthesis

Results for depressive symptoms and obsessive-compulsive symptoms are depicted in Fig. 2 and Table 2. Small non-significant effect sizes were found for depressive symptoms and for Y-BOCS total, as well as the obsession and compulsion subscales of the Y-BOCS (see also Figure S1 and S2). Meta-regression showed that age, treatment duration and dosage were not related to effect sizes found in the studies (all $p > .1$). Heterogeneity was high for all outcome measures, see Table 2. Egger's tests were not significant for any outcome measure.

### 3.3. Safety and tolerability

Adverse effects are reported in Table S3. Twenty-two out of the twenty-three included publications reported on experienced side effects. Only three studies reported serious adverse events, including one case of acute pancreatitis (Grant et al., 2014), one case of dyspnea (Farahzadi et al., 2018) and one case of severe nausea (Farahzadi et al., 2018; Niciu et al., 2014). Most studies reported no difference in frequency of adverse events between the riluzole and placebo arm (see Table S3). Two studies found significantly more side-effects in the riluzole group, including nausea ($n = 8$) (Lemmon et al., 2015; Pittenger et al., 2015), poor coordination ($n = 3$) (Pittenger et al., 2015), and increased appetite ($n = 12$) (Ghaleiha et al., 2013). Increased transaminases were reported in a total of seven patients.

## 4. Discussion

This study provides a systematic overview of current literature regarding efficacy of riluzole for psychiatric disorders.

Qualitative assessments of the studies included in the systematic review suggested some positive effects of riluzole on symptoms of ASD, substance abuse and psychosis spectrum disorders. Moreover, on a biological level, riluzole has been shown to decrease glutamate concentrations in 22q11DS. Because for each of these disorders, few RCTs were available, replication studies are needed to see whether these effects are robust.

In the quantitative analyses, seven studies were included that all compared riluzole to placebo in a double blind randomized controlled design. We found small, non-significant positive effects of riluzole on depressive and obsessive-compulsive symptoms. Age of the patient, dosage and treatment duration did not influence these effects. However, the number of studies that could be included in the quantitative analyses was limited, as a consequence, our meta-analytical estimates are affected by high uncertainty and should be considered as a preliminary synthesis of the available literature.

The greatest strength of the present study is that it provides an up-to-date, quantitative and qualitative overview of the literature regarding the efficacy of riluzole in psychiatric disorders. Though our results reveal no significant overall effects of riluzole, given the small number of studies that could be included in the quantitative analyses, our results do not exclude the possibility that in some cases riluzole can improve depressive or obsessive-compulsive symptoms. Furthermore, most studies assessed the use of riluzole as an augmentation strategy, while only a few trials assessed its use as monotherapy (Farahzadi et al., 2018; Lemmon et al., 2015; Park et al., 2017). Given that in the augmentation studies most patients required continued pharmacological treatment, it is likely that relatively ill patients were included in these trials, possibly even therapy-resistant patients who had not responded to first- or second- line treatment. Indeed, preliminary evidence suggests that riluzole may have a role in treatment-resistant schizophrenia (Pillinger et al., 2019). Whether modulation of the glutamate system (for example by riluzole) may be beneficial in early stages of psychiatric disorders has never been investigated. For ALS, riluzole has proven to be particularly effective both early and late in the disease (de Jongh et al., 2019). Thus, however, more research is required to prove its efficacy as a single treatment strategy, possibly at early disease stages.

Our knowledge of the role of the glutamate/GABA system in etiology of psychiatric disorders has advanced enormously over the past decades. This understanding allows for discovery of novel therapeutic strategies. A good example is the glutamate-enhancing drug ketamine, which is now recognized as an effective antidepressant (Murrough, 2016; Schwartz et al., 2016). There is mounting evidence that altered

balance between inhibition and excitation, or glutamatergic/GABA dysregulation, is involved not only in depression (McNally et al., 2008; Müller and Schwarz, 2007), but also in anxiety disorders (Bergink et al., 2004; Swanson et al., 2005), ASD (Ghanizadeh, 2013; Mariani et al., 2015; Penn, 2006; Ratajczak, 2011) and psychosis spectrum disorders (Hu et al., 2015; Poels et al., 2014; Uno and Coyle, 2019).

In our systematic review two out of the three studies reported positive effects of riluzole on irritability in ASD (Ghaleiha et al., 2013; Nicolson et al., 2017). At present, irritability in the context of ASD is treated with antipsychotics (NICE Clinical Guidelines, 2013). However, the use of antipsychotics in children and young people is associated with increased mortality (Ray et al., 2019). In this context, it may be worthwhile to further investigate the efficacy of riluzole for irritability in ASD (and related conditions) to examine whether riluzole has a better risk-/benefit balance than antipsychotics.

Riluzole may also be relevant as an augmentation strategy in psychotic disorders. A recent pharmacological challenge study in treatment-resistant schizophrenia patients showed a decrease in glutamate + glutamine (GLX) concentrations in the anterior cingulate cortex (ACC) after a 2-day riluzole challenge (Pillinger et al., 2019). In this study, higher baseline GLX concentrations were associated with more severe negative symptoms and worse verbal learning. Because the study used a non-randomized, non-blinded design, it was not included in the current systematic review.

Hopefully, in the near future more information will become available on effects of extended riluzole treatment in psychiatric disorders. This may inform whether riluzole is a useful augmentation or monotherapy strategy. In addition, pharmacological challenge studies using riluzole (Ajram, 2015; Vingerhoets et al., 2018) may increase our understanding of the glutamate/GABA system and its role in the pathophysiology of psychiatric disorders.

In conclusion, riluzole augmentation may be a useful pharmacological strategy for a variety of psychiatric disorders. Riluzole may have some positive effects on symptoms related to psychotic disorders, substance abuse disorders depression and OCD, and is reasonably well-tolerated. However, existing RCTs on riluzole are heterogeneous and only a limited number of studies is available for each psychiatric disorder. The results of the meta-analysis show no overall significant effect of riluzole on depressive and obsessive-compulsive symptoms. Future studies will need to establish whether there is a role for riluzole in the treatment of psychiatric disorders.

## Competing interests

The authors report no conflicts of interest.

## Contributions

J.B. and M.H. performed the systematic search and performed the analyses. J.B. and M.H. performed the critical appraisal and formatted the tables and figures. J.B wrote the initial version of this article; all authors reviewed and accepted the final version of the article.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.06.020.

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