Published in final edited form as:

Expert Opin Drug Metab Toxicol. 2008 September ; 4(9): 1223–1234. doi:10.1517/17425255.4.9.1223.

Riluzole in Psychiatry:

A Systematic Review of the Literature

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Abstract

Background—The glutamate system appears to be an important contributor to the pathophysiology of mood and anxiety disorders. Thus, glutamatergic modulators are reasonable candidate drugs to test in patients with mood and anxiety disorders. Riluzole, a neuroprotective agent with anticonvulsant properties approved for the treatment of amyotrophic lateral sclerosis (ALS) is one such agent.

Objective—To assess the potential risks and benefits of riluzole treatment in psychiatric patients.

Methods—A PubMed search was performed using the keywords “riluzole”, “inhibitor of glutamate release”, and “glutamatergic modulator” in order to identify all clinical studies and case reports involving riluzole in psychiatric patients.

Results/Conclusion—Riluzole’s side effect profile is favorable, and preliminary results regarding riluzole for the treatment of severe mood, anxiety, and impulsive disorders are encouraging.

Keywords

antidepressant; bipolar disorder; depression; glutamate; mania; plasticity; psychiatry; riluzole; anxiety disorder; treatment

1. Introduction

Riluzole, a neuroprotective agent with anticonvulsant properties, is a member of the benzothiazole class. Chemically, riluzole is 2-amino-6-(trifluoromethoxy) benzothiazole, and is the only drug currently approved (by the Food and Drug Administration (FDA) in the United States, the Committee on Proprietary Medicinal Products (CPMP) in Europe, and the Ministry of Health, Labor, and Welfare (MHW) in Japan) for the treatment of amyotrophic lateral sclerosis (ALS). Its use in other psychiatric or neurologic disorders is considered off-label.

Riluzole possesses both glutamatergic modulating, antiepileptic, and neuroprotective properties, all of which make it a promising candidate for the treatment of mood and anxiety disorders. An increasing number of publications regarding its use in neurodegenerative and psychiatric disorders are emerging. In this review, we investigate the pharmacology, pharmacokinetics, side effect profile, and presumptive mechanism of action of riluzole, as well as its use as a treatment in psychiatric disorders.

2. Method

A PubMed literature search was performed using the keywords “riluzole”, “inhibitor of glutamate release”, and “glutamatergic modulator”. These papers were then reviewed to identify all clinical studies in psychiatric populations. In addition, in order to assess potential risks and benefits not identified in psychiatric studies, a review of all clinical studies and case reports involving riluzole was undertaken.

3. Mechanism of Action

Before discussing the mechanism of action of riluzole, it is important to frame this discussion based on current theories on the etiology of depression and presumptive mechanism of action of effective antidepressants and mood stabilizers. Contemporary hypotheses of depression postulate that impairments in cellular resilience and plasticity occur in patients with severe and recurring mood disorders (major depressive disorder (MDD) and bipolar disorder (BPD)) [1]. These impairments are believed to result in atrophy of neurons in critical circuits that mediate hedonic drive, motor behavior emotions, cognition, etc. Thus, severe mood disorders are increasingly being seen as disorders of synapses and circuits rather than simply as the consequence of neurotransmitter alterations [2]. In support of this view, postmortem studies have shown decreases in the number, size, and density of neurons in key areas presumed to be involved in depression (e.g., anterior cingulate cortex, dorsolateral prefrontal cortex, orbitofrontal cortex) (reviewed in [3]). These anatomical changes on a tissue level are consistent with neuroimaging studies showing regional reductions in brain volume [4].

Several mechanisms are believed to result in impairments of cellular resilience and neuroplasticity, including stress, cortisol increases, reduced neurotrophic factors, and excess levels of glutamate. With regards to glutamate, its extracellular concentrations are tightly regulated; excesses are believed to result in neurotoxicity associated with neurodegenerative diseases, trauma, and ischemia. Thus, there has been a recent focus on the development of glutamatergic modulators in the hopes that their neuroprotective properties would be beneficial for these conditions. Such neuroprotective agents could be effective by more tightly regulating glutamate concentrations to minimize glutamate's deleterious effects on neurons and glia in depression, and by enhancing adequate trophic support so that the intracellular signaling changes required for antidepressant action take place.

Riluzole is a glutamatergic modulator with neuroprotective and plasticity-enhancing properties and for these reasons could potentially play an important role in the treatment of mood and anxiety disorders. Evidence supporting the favorable CNS therapeutic profile of riluzole includes a growing body of work showing that this agent has neuroprotective properties in animal models of brain ischemia [5], spinal cord injury [6,7], traumatic brain injury [8], Parkinson's disease [8], post-traumatic peripheral neuropathy [9], and acute noise-induced hearing loss [10]. It has been suggested that inhibition of tyrosine phosphorylation (which is observed in response to brain ischemia) may contribute to riluzole's neuroprotective properties against excitotoxic injury [11]. In addition, riluzole 10 M was found to be neuroprotective in glutamate-induced toxicity in primary glial cell culture, as evidenced by decreases in lactate dehydrogenase activity and nitrite levels [12].

Although the evidence for riluzole's neuroprotective effects in the preclinical models cited above is robust, evidence in humans is mixed. There are positive controlled trials for riluzole's use in ALS [13,14], and negative studies for its use in Huntington's disease [15], multiple system atrophy [16], and Parkinson's disease [17]. Trials to assess its effectiveness in other neurodegenerative conditions studies are underway. In one study involving 14 patients with multiple sclerosis, riluzole showed neuroprotective properties as evidenced by a reduced rate of cervical cord atrophy and development of hypointense T1 brain lesions on magnetic resonance imaging (MRI) [18].

Table 1 lists the different mechanisms of action that have been ascribed to riluzole, some of which might explain its antidepressant effects. However, it is unknown which of them is directly relevant to its potentially mood-enhancing effects. The strongest evidence for riluzole's mood enhancing and anxiolytic effects come from its action on the glutamatergic system, presumptively involving its glutamate inhibitory release, alpha-amino-3-hydroxy-5-

methyl-4-isoxazolepropionic acid (AMPA, a post-synaptic glutamate receptor) trafficking, and glutamate reuptake properties. Discerning which of these mechanisms within the glutamatergic system is important or relevant to the antidepressant and anxiolytic properties of riluzole is still unknown. Few preclinical studies have attempted to discern what mechanisms might be relevant to riluzole's therapeutic effects in the context of depression and anxiety models; such studies are currently underway.

3.1 Regulation of Extracellular Glutamate

3.1.1. Inhibition of glutamate release—Riluzole inhibits the release of glutamate as evidenced by its ability to reduce K^+ -evoked release from slices of hippocampal area CA1 [19] and rat cortical synaptosomes [20].

3.1.2 Enhancing glutamate transporter reuptake—The excitatory amino acid transporters (EAATs), a family of sodium-dependent carrier proteins, are also capable of regulating glutamate synaptic levels. The mechanism whereby this uptake process occurs is uncertain, but a recent report identified riluzole's ability to increase GLT1 expression (also known as EAAT2, the physiologically dominant astroglial protein (G. Sanacora, unpublished findings)) as a possibility [21]. More recently it was reported that riluzole enhances the activity of the glutamate transporters GLAST, GLT1, and EAAC1 [22]. In this study, concentrations of riluzole ranging from 0.01 to 100 μ M increased specific glutamate uptake in HEK_{GLT1}, HEK_{EAAC1}, and HEK_{GLAST} in a dose-dependent fashion; at the highest concentrations the increase was about 30% in the three cell lines. The authors speculated that riluzole acts by changing the relative affinity for glutamate rather than modifying the expression or the trafficking of transporters, as indicated by the lack of change or the small changes in the maximal uptake rate in the different cell lines [22]. Azbill and colleagues (2000) reported that 0.1 and 1 μ M riluzole significantly increased glutamate uptake *in vitro* and after *in vivo* treatment in animals [23]. Dunlop and colleagues (2003) found a 20-25% increase in glutamate uptake in rat spinal cord synaptosomes at higher riluzole concentrations (10 to 300 μ M) [24]. Finally, Frizzo and colleagues (2004) reported that riluzole had a biphasic effect with significant increases in uptake at 1 and 10 μ M (15%); higher concentrations were found to be ineffective or even toxic in astrocyte cultures [25].

3.1.3 Increasing AMPA trafficking—Of the glutamatergic drugs available for study in mood disorders, riluzole has particularly diverse effects within the glutamatergic system, including inhibition of glutamate release, AMPA trafficking (involved in synaptic plasticity), and enhancement of glutamate reuptake. Riluzole also affects AMPA receptors by increasing cell surface expression of the AMPA subunits GLUR1 and GLUR2, and inducing changes involved in AMPA trafficking; the latter is a component of synaptic plasticity [26]. It has no known direct effects on NMDA or kainate receptors [27].

As will be discussed below, studies indicate that riluzole might have antidepressant properties. Because all FDA-approved antidepressants affect serotonin and/or norepinephrine, it would be important to determine whether riluzole modulates these same neurotransmitters and if it does, whether this effect could possibly explain its antidepressant properties. Riluzole has been found to strongly attenuate electrically evoked release of dopamine and norepinephrine but not serotonin; such neurotransmitters have been widely implicated in the mechanism of antidepressant action [28].

3.2 Regulation of Neurotrophic Factors

3.2.1. Increasing vascular endothelial growth factor (VEGF)—VEGF has been implicated in neuronal survival, neuroprotection, regeneration, growth, differentiation, and axonal outgrowth, all of which are associated with the pathophysiology of MDD [29]. Recently,

VEGF mRNA levels in the peripheral leukocytes of 32 drug-naïve patients with MDD were found to be significantly higher than those from a group of age- and sex-matched controls; furthermore, the magnitude of the decrease of VEGF mRNA after eight weeks of treatment with paroxetine (10-40 mg/day) significantly correlated with clinical improvement [30]. However, no association was found between two single nucleotide polymorphic markers of the VEGF gene and MDD or its clinical subtypes [30]. The results of this study are in contrast to the finding that stress decreases levels of VEGF in the adult hippocampus [31] and that VEGF signaling is necessary for the behavioral actions of antidepressants [32]. A recent study found that riluzole injection (10 mg/kg/d, IP) for five days significantly reversed insulin increases in VEGF levels in oxygen-induced retinopathy in rats; its consequences included retinal hemorrhage in rat pups [33].

3.2.2. Brain Derived Neurotrophic Factor (BDNF)—Riluzole stimulates nerve growth factor, brain derived growth factor, and glia cell line-derived neurotrophic factor synthesis in cultured mouse astrocytes [34]. Another report found that repeated, but not single, injections of riluzole resulted in prolonged elevation of hippocampal BDNF, and were associated with increased numbers of newly generated cells in the granule cell layer [35].

4. Clinical Studies in Psychiatry

Although multiple studies have been conducted with riluzole in a number of psychiatric conditions, it is currently only indicated for use in ALS

Riluzole easily crosses the blood brain barrier [36] and ample long-term safety data exist concerning its use in humans. Riluzole has been reported to be well-tolerated for long periods of up to almost seven years [37]. Evidence from a variety of studies with experimental animals and with humans indicates that it is devoid of the psychotomimetic or other behavioral side-effects commonly associated with excitatory amino acid antagonists. Clinical use and clinical investigations support riluzole's antidepressant and anxiety properties (see Table 2). These reports comprise either case series or open-label studies in patients with treatment-resistant conditions, including unipolar and bipolar depression, generalized anxiety disorders, obsessive-compulsive spectrum disorders, and cocaine dependence. Controlled studies, which are needed to confirm these preliminary findings, are currently underway.

4.1 Mood disorders

Preclinical studies support the antidepressant properties of riluzole as evidenced by its antidepressant-like effects in the unpredictable stress paradigm [38].

A case report indicated successful augmentation therapy with riluzole in a patient with treatment-resistant bipolar depression who had developed a severe rash from lamotrigine [39]. This case report was followed by a six-week open label monotherapy study with riluzole in 19 patients with treatment-resistant MDD; riluzole at a mean daily dose of 169 mg/day had significant antidepressant effects [40]. Subsequently, riluzole was studied in 14 patients with bipolar depression of moderate severity who had failed to respond to a prospective trial of lithium within therapeutic levels. Augmentation of lithium with riluzole (mean daily dose 171 mg) for eight weeks resulted in significantly improved depressive symptoms [41]. In this small study, there was no evidence of hypomania or mania. Finally, in a recent trial, riluzole (mean dose 95 mg/day) was added to ongoing antidepressant therapy in 10 patients with treatment-resistant MDD; these patients showed significant improvement in depressive symptoms after six to 12 weeks [42]. Notably, antidepressant response in these studies occurred within the first few weeks of starting riluzole. The most common side effects were fatigue, nausea, and weight loss.

In an attempt to better understand the trajectory of response to riluzole in depression and the factors predictive of response, data from the two studies discussed above were pooled [40, 41]. This group comprised 33 patients aged 18-70 years who were treated for six weeks with riluzole (50 to 200mg/day) in monotherapy (for MDD) or in combination with lithium for bipolar depression. Response to riluzole was apparent at week one and remained significant for six weeks (the endpoint for the study with MDD patients, and the timepoint at which the eight-week study of bipolar depression patients was thus stopped). The mean daily dose leading to antidepressant response was 170 mg for both studies.

Several demographic and clinical factors were examined as predictors of response for patients with unipolar (n=19) and bipolar depression (n=14). However, none were associated with change in Montgomery-Asberg Depression Rating Scale (MADRS) scores. Pearson's correlation for these factors was male gender (0.22), age (0.014), unipolar and bipolar diagnosis, (0.156), duration of current major episode (-0.15), past substance abuse or dependence (0.107), melancholic features (-0.003), atypical depression (0.055), mean daily dose of riluzole (0.162), and MADRS score at baseline (0.33).

Riluzole has not yet been studied in mania. Riluzole's antidepressant properties in bipolar depression and its ability to reduce amphetamine hyperactivity (an animal model of mania) suggest that it should be considered for further testing for this facet of BPD. Notably, in mice, pretreatment with 10 mg/kg, but not 3 mg/kg, of riluzole moderately decreased amphetamine- (but not MK-801-) induced hyperlocomotion [43].

Although studies of riluzole's efficacy as a treatment for anxiety disorders will be reviewed in greater detail below, it is worth noting that the above-mentioned analysis of the combined dataset involving 33 patients also assessed changes in anxiety symptoms, as they are highly prevalent during depressive episodes. Furthermore, such anxiety changes have been associated with a worse outcome, as indicated by an increased risk for relapse, suicide, and functional disability; a significant proportion of patients presenting with depression and anxiety have poor outcome related to residual and/or refractory anxiety, increased risk of suicidality, and poor treatment response [44-49]. In the merged dataset, a significant improvement in anxiety symptoms was found from week two to study endpoint.

Interestingly, both riluzole and lamotrigine (the latter is approved for relapse prevention in BPD) are inhibitors of glutamate release and have anticonvulsant and neuroprotective properties. Although they share several preclinical findings, they are clinically dissimilar. Unlike lamotrigine, riluzole does not require dose titration, nor has it been associated with severe skin rash (see Table 3). Nevertheless, riluzole has not yet been submitted to the same rigorous mood disorders research as lamotrigine. Additional controlled studies with riluzole in mood and anxiety disorders are needed.

4.2 Generalized Anxiety Disorders (GAD)

The anti-anxiety effects of riluzole have been postulated to be the result of postsynaptic GABAA receptor function potentiation in hippocampal neurons [50]. In preclinical work, an earlier report described the anxiolytic effects of riluzole as evidenced by the antagonism of the anxiogenic properties of beta-carboline FG 7142 [51]. A more recent study found that riluzole 3-30 mg/kg p.o. had anxiolytic effects in the rat-conditioned emotional response model of anxiety [52].

The hypothalamic-pituitary-adrenal (HPA) axis hormones are often studied to determine the effects of a particular compound on stress as a model of anxiolytic effects. Riluzole had no significant effects on HPA system activity under baseline and cognitive-stress induced conditions in healthy elderly subjects. However, there was a trend for dampening of the

endocrine responses (ACTH, cortisol) [53]. How this finding would translate to patients with anxiety disorders remains to be determined.

Recently, Mathew and colleagues (2008) found, in an eight-week open-label study, that riluzole 100 mg/day was effective in treating anxiety symptoms in patients with GAD. In this study, 80% of completers responded to riluzole, and 53% met remission criteria at eight weeks [54]. In the same study, it was found that hippocampal NAA concentration changes were greater in responders to riluzole than in non-responders.

4.3 Obsessive-Compulsive Spectrum Disorders

In a patient diagnosed with obsessive-compulsive disorder (OCD) and MDD, significant anti-obsessional and antidepressant effects were noted with eight weeks of riluzole treatment (50 mg BID) added to the ongoing medication regimen [55]. Coric and colleagues examined riluzole in an open-label study in 13 patients with treatment-resistant OCD. Riluzole was prescribed at 50 mg BID for six to 12 weeks and 54% of subjects demonstrated a >35% reduction in Y-BOCS scores [56]. More recently, Grant and colleagues [57] found that 12 weeks of open-label treatment with riluzole 50 mg BID was effective in the treatment of OCD in six children aged eight to 16 years. In contrast, in animal studies, riluzole 0.3-10 mg/kg i.p. in mice had no effect on marble-burying behavior, an animal model of OCD [58].

In a recent letter to the editor, it was reported that riluzole 100 mg BID added to fluoxetine ameliorated symptoms of disordered eating, pathological skin picking, depression, obsessions, and compulsions in a 52 year old woman with a diagnosis of OCD, MDD, and anorexia nervosa [59]. In another case report, riluzole at doses up to 200 mg/day was found to improve symptoms of trichotillomania [60]. Improvements have also been reported with riluzole in compulsive skin picking [59] and compulsive self-injurious behavior [61]. For more information the reader is referred to a comprehensive review on the topic of OCD [62].

4.4 Cocaine Dependence

In a multi-arm, modified blinded, placebo-controlled screening trial of patients with cocaine dependence, riluzole 100 mg/day had no beneficial effects [63].

5. Side Effect Profile

Controlled studies in ill patients taking multiple concomitant medications indicate that riluzole is well-tolerated [64]. The most frequent dose-related adverse events include nausea, asthenia, and elevated liver enzyme levels. Nausea was reported by 12 to 21% of riluzole-treated patients, compared with 12% for placebo [14]. Less than 1% of patients with asthenia discontinued treatment. Dizziness, diarrhea, anorexia, and circumoral paresthesia occurred more frequently with 200-mg/day of riluzole. It should be noted that concomitant medications were permitted in the trials that examined riluzole, thus adverse events for riluzole may be over-attributed (approximately 72% of subjects took at least one concomitant medication; the mean number of concomitant medications per patient during this trial period was 6.6). Elevated alanine transaminase levels accounted for most treatment discontinuations based on laboratory adverse events. This represented less than four percent of any treatment group (50 mg, 100 mg, or 200 mg riluzole) [14]. In 169 patients with ALS, high inter-individual variability in riluzole serum concentrations was noted. For instance, patients with high serum levels and area under the curve per kilogram of body weight more often had diarrhea [65].

In clinical trials of riluzole for mood disorders, the most common adverse events were headache, fatigue, gastrointestinal distress (nausea or vomiting), decreased salivation, constipation, and tension/inner unrest [64]. In a few patients, a reversible increase in liver function tests was also seen; similar side effects have been observed in ALS trials [13]. No

serious adverse events with riluzole have been reported in studies of adults or children with mood or anxiety disorders.

Riluzole has been associated with rare life-threatening events. One case consisted of a 50-year-old man diagnosed with ALS who, 14 days after starting riluzole 50 mg BID, developed myalgia, fever, and increased liver function tests. In this case, a hypersensitivity reaction (myalgia, fever, rash, increased liver function tests, pericarditis) to riluzole was diagnosed [66]. Another report mentions the onset of hallucinations one week after riluzole 50 mg BID was added to memantine and bupropion in a 43-year old woman with a long history of treatment-resistant MDD [67]. There have also been case reports of acute hepatitis [68], pancreatitis [69], and hypersensitivity pneumonitis [70]. Two cases of methemoglobinemia have also been reported [71,72]. The literature review also found reports that riluzole increases blood pressure in patients with multiple system atrophy and ALS [73,74], however, this risk does not appear to be significantly increased in individuals without this disease. Granulocytopenia was described in three patients out of 4000 taking riluzole [75]. More recently, another case of reversible granulocytopenia two weeks after starting riluzole was reported [76].

6. Dosing, Pharmacokinetics, and Drug Interactions

6.1 Dosing

The optimal dose of riluzole in ALS is 100 mg/day given BID. However, in studies involving adults with a psychiatric disorder, the dose of riluzole typically ranged from 100-200 mg/day (again, this dosage and use are off-label). Most published reports in patients with mood disorders used flexible dosing up to 200 mg/day. Fixed doses of 100 mg/day were generally used in OCD with a few exceptions. In children with OCD, the dose of riluzole was initiated at 10 mg/day and increased by 10 mg every few days with the mode dose being 100 mg/day [57]. Table 2 contains a summary of riluzole dosing in these studies. Because the majority of the trials conducted in psychiatry used doses higher than that considered optimal in ALS, future studies will need to determine whether a higher dose offers any advantage, particularly because there is a dose-dependent risk for increases in transaminases and gastrointestinal disturbances.

6.2 Pharmacokinetics

The time to peak concentration of riluzole is one to 1.5 hours, and a maximum serum concentration of 214 ng/ml has been reported after a single 50 mg oral dose [77]. The bioavailability of riluzole is 60% (range 30% to 100%) [77], and its total protein binding is 97.5%. Riluzole is extensively metabolized in the liver (Prod Info Rilutek(R), 2006) by direct glucuronidation and hydroxylation by the cytochrome P450IA2 enzyme (CYP1A2) (Prod Info Rilutek(R), 2006). The metabolism of riluzole results in N-hydroxyriluzole and glucuronide conjugates, both of which are inactive. Approximately 85% to 95% of a 50 mg oral tablet is eliminated in the urine in the first 24 hours, and almost all of the metabolites are excreted in the urine. Less than 10% is excreted in feces. It is unknown if riluzole is excreted into human breast milk. The elimination half-life is 12 to 14 hours.

Pharmacokinetic studies of riluzole show a large inter-individual variability in the drug's clearance and serum concentrations, and food decreases absorption. The inter-individual variability of riluzole's peak was reported to be as high as 74% [78]. An *in vitro* study of riluzole metabolism in liver and yeast microsomes revealed that riluzole is transformed to N-hydroxyriluzole by cytochrome P450 enzyme subform 1A5 (CYP1A2) and by glucuronidation to an unidentified metabolite [79]. *In vivo* studies addressing glucuronidation of riluzole are lacking. In a previous study of ALS patients using caffeine as a metabolic probe, it was found that differential CYP1A2 activity was responsible for 37% of the observed variability in

riluzole clearance [80]. A recent study did not find that genetic variations in CYP1A1 and CYP1A2 genes seemed to influence riluzole levels [81]. Therefore, alternative metabolic pathways, such as glucuronidation, may also play a role in the inter-individual variability of riluzole elimination.

Glucuronidation is catalyzed by a family of uridine-diphosphate-glucuronosyltransferases (UGTs). These enzymes are responsible for the conjugation of glucuronic acid with many endogenous (e.g., bilirubin, steroids) and xenobiotic compounds [82]. Several subforms of UGT have been identified with both hepatic and intestinal expression sites [83]. The UGT1A1 subform has a genetic polymorphism that results in decreased gene expression. The UGT1A1 wildtype has a six-fold TA repeat ((TA)₆) in the promoter region of the UGT gene, while increasing numbers of tandem repeats ((TA)₇, designated as UGT1A1*28), result in decreased expression. So far this is the only functional genetic polymorphism that has been elucidated for UGT [84].

Recent evidence suggests that glucuronidation is a major metabolic pathway. Limited data are available on the *in vivo* metabolic elimination of riluzole. *In vitro* experiments suggest that CYP1A2 seems to be mainly involved in riluzole clearance. However, *in vitro* studies also suggest that formation of riluzole-glucuronide plays a prominent role and may, to some extent, determine the drug's pharmacokinetic variability in patients. It is yet unknown whether riluzole-glucuronide has any therapeutic effect, and how this relates to the effect of the parent compound [81]. However, genetic variability in UGT1A1 was reported not to be the reason for inter-individual variability in riluzole serum concentrations [81].

In terms of brain penetrance, Colovic and colleagues previously reported that riluzole is distributed to brain when administered orally [85,86]. More recently, it was reported that riluzole is transported by p-gp at the blood brain barrier level [87]. The comparison between brain/plasma concentration ratios in CF1 *mdr1a* (-/-) and *mdr1a* (+/+) mice was 1.4 for riluzole. At least in ALS, transport out of the brain through p-gp could, at least in part, explain why riluzole plasma level does not always correlate with therapeutic effects or side effects. The relevance between p-gp and clinical response or side effects in psychiatric disorders is currently unknown.

6.3 Drug interactions with riluzole

The following drugs are metabolized by cytochrome P450: amitriptyline, imipramine, chlordiazepoxide, ciprofloxacin, digoxin, norfloxacin, phenacetin, rifampin, sulfasalazine, and tacrine. There is thus a theoretical risk of drug toxicity when they are used in combination with riluzole.

7. Conclusion

Riluzole, a neuroprotective agent with anticonvulsant properties, appears to be a promising candidate drug for the treatment of neuropsychiatric disorders; however this remains to be proven. It is a glutamatergic modulator with diverse effects within the glutamatergic brain system, a system that is being increasingly linked with the pathophysiology of mood and anxiety disorders. Riluzole's side effect profile is favorable, and preliminary studies in severe mood, anxiety, and impulsive disorders are encouraging. These initial trials will need to be followed by more rigorous controlled studies to confirm the nature and extent of riluzole's therapeutic effects. Riluzole has already led to essential insights into the role of the glutamatergic system in the mechanism of action of antidepressants.

8. Expert opinion

Contemporary theories of mood disorders note that they are characterized by disruptions in cellular resilience and neuroplasticity. Disruptions in neuroplasticity are believed to be largely due to alterations in CNS glutamate neurotransmission. Riluzole is among a series of candidate glutamatergic modulators that is being actively explored for use in a variety of neuropsychiatric disorders; it appears to modulate many different aspects of glutamate's regulatory system. Riluzole has proved ineffective in some trials of neurodegenerative conditions such as Huntington's disease, multiple system atrophy, and Parkinson's disease; although the reason for these failed trials is unknown, it is possible that glutamatergic modulation with an agent such as riluzole would be more useful in individuals earlier in the disease process rather than later.

Riluzole is currently afforded orphan drug status and is approved (by the Food and Drug Administration (FDA) in the United States, the Committee on Proprietary Medicinal Products (CPMP) in Europe, and the Ministry of Health, Labor, and Welfare (MHW) in Japan) only for the treatment of ALS. At present, it is quite expensive, and insurance coverage for this drug is mainly for patients with ALS. For that reason, its use in a clinical population for patients with psychiatric disorders is limited at this time and off-label. Controlled studies, though lacking, are currently underway. Positive results in patients with mood and anxiety disorders would certainly impact riluzole's clinical use and further testing in psychiatric disorders. Finally, much is being learned from riluzole in preclinical and clinical studies. When it becomes generic, or when new, improved versions of it become available, riluzole will undoubtedly have both short- and long-term significance in the treatment of psychiatric disorders.

Acknowledgments

The authors would like to acknowledge the support of the Intramural Research Program of the National Institute of Mental Health, the Stanley Medical Research Institute and NARSAD. Ioline Henter provided outstanding editorial assistance.

Conflict of Interest

The authors would like to acknowledge the support of the Intramural Research Program of the National Institute of Mental Health. The authors declare that, except for income received from our primary employer, no financial support or compensation has been received from any individual or corporate entity over the past three years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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Table 1

Mechanisms of action for riluzole

Mechanism of action	References
Inhibited release of glutamate as evidenced by its ability to reduce K^+ -evoked release from slices of hippocampal area CA1	[19]
Inhibited release of glutamate as evidenced by its ability to reduce K^+ -evoked release from rat cortical synaptosomes	[20]
Inactivation of voltage-dependent sodium channels	[88]
Inactivation of P/Q-type calcium channels	[89]
Direct PKC inhibition	[90]
AMPA receptor potentiation	[26]
Potentiation of postsynaptic GABA(A) receptor function	[50]
Suppression of HPA axis	[53]
Stimulation of NGF, BDNF, and GDNF in cultured mouse astrocytes	[34]
Increased clearance of glutamate from synaptic space through enhancement of reuptake in rat astrocytes	[25]
Enhanced high-affinity glutamate uptake in rat spinal cord synaptosomes <i>in vitro</i> and after treatment <i>in vivo</i>	[23]
Inhibition of glutamate release from presynaptic terminals through a mechanism linked to G-protein signaling	[89]
Activation of TREK, a member of the two-pore domain potassium (K2P) channel	[91]
Increased GLT1 expression (also known as EAAT2, the physiologically dominant astroglial protein (G. Sanacora, unpublished findings)	[21]
Enhanced activity of glutamate transporters GLAST, GLT1 and EAAC1	[22]

Table 2
Clinical studies of riluzole in treatment-resistant neuropsychiatric patients

Authors	Study design	Study Population/n	Dose (all given BID)	Findings	References
Mood Disorders					
Singh et al 2004	Case report, add-on	Bipolar depression, n=1	200 mg/day	Successful augmentation therapy with riluzole in a patient with treatment-resistant bipolar depression who developed a severe rash from lamotrigine	[39]
Zarate et al 2004	Open-label for 6-weeks, 2wk washout, monotherapy	MDD, n=19	Mean dose 169 mg/day	6-week open label monotherapy study in 19 patients with treatment-resistant MDD. Riluzole had significant antidepressant effects	[40]
Zarate et al 2005	Open-label for 8 wks, add-on to lithium, wk washout from other antidepressants	Bipolar depression, n=14	Mean dose 171 mg/day	In 14 patients with bipolar depression of moderate severity who had failed to respond to a prospective trial of therapeutic levels of lithium, augmentation of lithium with riluzole for 8 weeks significantly improved depressive symptoms.	[41]
Sanacora et al 2007	Open-label, no washout, add-on	MDD, n=10	Mean dose 95 mg/day	When added to ongoing antidepressant therapy in 10 patients with treatment-resistant MDD, led to significant improvements in depressive symptoms after 6-12 weeks	[42]
Obsessive-Compulsive Spectrum Disorders					
Coric et al 2003	Case report, no washout, add-on	MDD and OCD, n=1	100 mg/day	In a patient diagnosed with OCD and MDD, significant anti-obsessional and antidepressant effects were noted with eight weeks of riluzole (50 mg bid) treatment when added to the ongoing medication regimen	[55]
Coric et al. 2005	Open-label, 6-12 wks	OCD, n=13	100 mg/day	7/13 (54%) demonstrated a >35% reduction in Y-BOCS scores, and 5/13 (39%) were responders. HAM-D and HAM-A scores for the group also significantly improved over time. Riluzole was well tolerated with no serious adverse effects noted.	[56]
Grant et al. 2007	Open-label for 12 wks, no washout, add-on psychotropics 4/6, K-SADS	OCD in children, n=6	10 mg increased every few days, and in 2 cases the dose exceeded 120 mg/day; all subjects except one took at least 50 mg BID	6 subjects, ages 8-16 years received 12-weeks of open-label riluzole 50 mg BID added to ongoing treatment. 4/6 subjects had clear benefit with reduction of more than 46% (39% overall on the Children's Yale-Brown Obsessive-Compulsive Scale and "Much Improved" or "Very Much Improved" on the Clinical Global Impressions-Improvement scale; there were no adverse effects leading to discontinuation or dose reduction	[57]
Generalized Anxiety Disorder					
Mathew et al. 2005	Open-label for 8 wks treatment in GAD patients	GAD, n=18	100 mg/day	12/15 patients who completed the trial responded to riluzole. At 8 weeks, 8/15 achieved remission of their anxiety. The median time to response was 2.5 weeks	[92]
Case report/series					
Pittenger et al. 2005	Cases of patients with self-injurious behavior	25 yo woman with PTSD and BPD; 45 yo woman with MDD, OCD and GAD, n=2	50 mg BID	25 yo woman with PTSD and BPD had no more cutting after 6 wks on riluzole at 50 mg bid added to other medications; 45 yo woman with MDD, OCD and GAD. Hitting and cutting self ceased after 4 wks on riluzole 50 mg bid added to ongoing meds and remained improved 6 months later	[61]
Sasso et al. 2006	Case report, add-on to fluoxetine	OCD, MDD, and anorexia nervosa, n=1	200 mg/day	Significant improvement in symptoms of eating disorder, pathological skin picking, depression, obsessions and compulsions by 4 wks	[59]
Coric et al. 2007	Case report, riluzole added to citalopram	Trichotillomania and depression, n=1	Up to 200 mg/day	At 16 weeks HAM-D score was 7, down from 26 at baseline; at 72 weeks symptoms (depression and urge to pull hair) continued to be minimal	[60]

Table 3**Comparison of riluzole and lamotrigine**

	Riluzole	Lamotrigine
Neuroprotective	Yes	Yes
Anticonvulsant	Yes	Yes
Efficacy in acute MDD	Yes (only open-label studies)	? Yes (the majority of controlled studies are not positive; clear evidence in maintenance treatment)
Inhibition of voltage-gated Na ⁺ channels	Yes	Yes
Ca ²⁺ channel blockade	Yes (P/Q type)	Yes (N- and P-type)
AMPA potentiator	Yes	Yes
Increased expression of BDNF	Yes	??
Dose titration	None or rapid	Very slow
Steven-Johnson's syndrome	No	Yes
Response to the other agent	3 out of 4 lamotrigine responders responded to riluzole	?