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Riluzole in the Treatment of Mood and Anxiety Disorders

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Abstract

Recent advances implicate amino acid neurotransmission in the pathophysiology and treatment of mood and anxiety disorders. Riluzole, which is approved and marketed for the treatment of amyotrophic lateral sclerosis, is thought to be neuroprotective through its modulation of glutamatergic neurotransmission. Riluzole has multiple molecular actions *in vitro*; the two that have been documented to occur at physiologically realistic drug concentrations and are therefore most likely to be clinically relevant are inhibition of certain voltage-gated sodium channels, which can lead to reduced neurotransmitter release, and enhanced astrocytic uptake of extracellular glutamate.

Although double-blind, placebo-controlled trials are lacking, several open-label trials have suggested that riluzole, either as monotherapy or as augmentation of standard therapy, reduces symptoms of obsessive-compulsive disorder, unipolar and bipolar depression, and generalized anxiety disorder. In studies of psychiatrically ill patients conducted to date, the drug has been quite well tolerated; common adverse effects include nausea and sedation. Elevation of liver function tests is common and necessitates periodic monitoring, but has been without clinical consequence in studies conducted to date in psychiatric populations. Case reports suggest utility in other conditions, including trichotillomania and self-injurious behaviour associated with borderline personality disorder. Riluzole may hold promise for the treatment of several psychiatric conditions, possibly through its ability to modulate pathologically dysregulated glutamate levels, and merits further investigation.

Until very recently, aetiological theories of psychiatric pathophysiology have focused on the brain's modulatory monoamine systems – dopamine, serotonin and norepinephrine.[1] With the exception of lithium, benzodiazepines and antiepileptic medications, all US FDA-approved treatments for mood and anxiety disorders target these monoaminergic neurotransmitters. However, recent large-scale effectiveness trials performed in patients with mood and anxiety disorders have highlighted the limitations of medications that target brain monoamines. For example, the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial of treatments for major depressive disorder found remission rates of only 37% after initial treatment and an additional 31% after a first switch to another treatment modality.[2] The need for more effective pharmacotherapies for mood and anxiety disorders, combined with a growing appreciation of the inadequacies of monoaminergic pathophysiological hypotheses, has led to the exploration of novel pathophysiological and therapeutic mechanisms.[3]

Dysregulation of the most common excitatory neurotransmitter, glutamate, appears to be central to the pathophysiology of mood and anxiety disorders.[4-7] This observation now motivates the investigation of glutamate-modulating agents as novel therapeutic tools in a variety of contexts.

Considerable recent attention has focused on riluzole (2-amino-6-trifluoromethoxy benzothiazole; Rilutek® [1], Sanofi-Aventis, Paris, France; figure 1), an 'orphan' drug that reduces glutamatergic overstimulation by several mechanisms. Riluzole is approved by the FDA for the treatment of amyotrophic lateral sclerosis (ALS); it remains the only medication proven to lengthen life and delay hospitalization in this disease.[8-10] Because of its glutamate-modulating properties, a number of groups have investigated the efficacy of riluzole in the treatment of several mood and anxiety disorders. While no definitive double-blind, placebo-controlled studies have been published to date, promising open-label reports provide preliminary evidence of the efficacy of riluzole in treatment-resistant major depressive disorder,[11-13] bipolar depression,[14] ob-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

sessive-compulsive disorder (OCD)[15-18] and generalized anxiety disorder (GAD).[19]

In this review, we present the evidence suggesting that riluzole may have utility in the treatment of mood and anxiety disorders, and merits further investigation in controlled studies. We review the various pharmacological effects of riluzole that have been described; because the drug has been shown to interact with multiple aspects of glutamatergic neurotransmission and homeostasis, this discussion is embedded in a review of the cogent aspects of the use and regulation of glutamate in the brain. We highlight the ability of this medication to enhance glial glutamate uptake, which may represent its most unique pharmacological property. We briefly review the established and investigational uses of riluzole in ALS and other neurological diseases. Next, we summarize the preliminary clinical evidence that riluzole has efficacy in depression, bipolar depression, OCD, GAD and other conditions. Finally, we discuss safety considerations and other practical matters arising in the use of riluzole in various clinical populations. We suggest that riluzole may be a prototype for other treatments for mood and anxiety disorders that work by enhancing glial glutamate uptake.

1. The Pharmacological Actions of Riluzole

1.1 Effects of Riluzole on Glutamatergic Neurotransmission and Homeostasis

Riluzole was initially developed as an anticonvulsant,[20,21] although it never received FDA approval for this use. Riluzole is marketed for use in ALS; it has been approved for this indication in the US and, more recently, in Australia, Canada and many European countries.[10] Riluzole has been found to be neuroprotective in animal models of several neurodegenerative diseases, including Parkinson's disease,[22-25] Huntington's disease,[26,27]

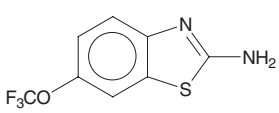

Fig. 1. Chemical structure of riluzole (2-amino-6-trifluoromethoxy benzothiazole).

ALS,[28] traumatic brain and spinal cord injury,[29-34] excitotoxicity[35,36] and cerebral ischaemia.[35,37-40] The neuroprotective properties of riluzole likely derive from its modulation of glutamatergic neurotransmission.

Glutamate is the major excitatory neurotransmitter in the adult brain. It is present in the CNS and CSF at high levels of 8–10 mmol/kg or even higher.[41-43] Glutamatergic projections participate in virtually all circuits in the adult CNS, including intracortical connections, cortical-subcortical connections and subcortical systems such as the basal ganglia, cerebellum, thalamus and brainstem structures.[44] Riluzole has been shown to affect several aspects of glutamatergic synaptic transmission, including release, postsynaptic effects and homeostatic regulation (see figure 2 and the discussion in sections 1.1.1–1.1.5). However, many of these varied pharmacological actions have been demonstrated only *in vitro*, at riluzole concentrations that are unlikely to be achieved in the brains of patients taking the drug. Those actions shown to occur at physiologically realistic drug concentrations are correspondingly more likely to contribute to the pharmacological effects of riluzole *in vivo* (see table I and sections 1.1.1–1.1.5).

1.1.1 Glutamate Release

Glutamate functions as a classical neurotransmitter (figure 2). Glutamate is packaged into vesicles at the synaptic termini of glutamatergic neurons. When an action potential reaches the axon terminal and depolarizes the membrane, it activates voltage-gated sodium channels and voltage-gated calcium channels (VGCCs). The resulting influx of sodium further depolarizes the axon terminal, while the influx of calcium activates synaptic release through interactions with SNARE proteins which, when activated, trigger fusion of neurotransmitter-containing vesicles with the presynaptic membrane. Glutamate-containing synaptic vesicles fuse with the presynaptic membrane, releasing their contents into the synaptic cleft. Glutamate rapidly diffuses across the synaptic cleft, where it can bind to postsynaptic receptors. Glutamatergic neurons are frequently projection neurons whose axons extend to distant sites within the CNS.[44]

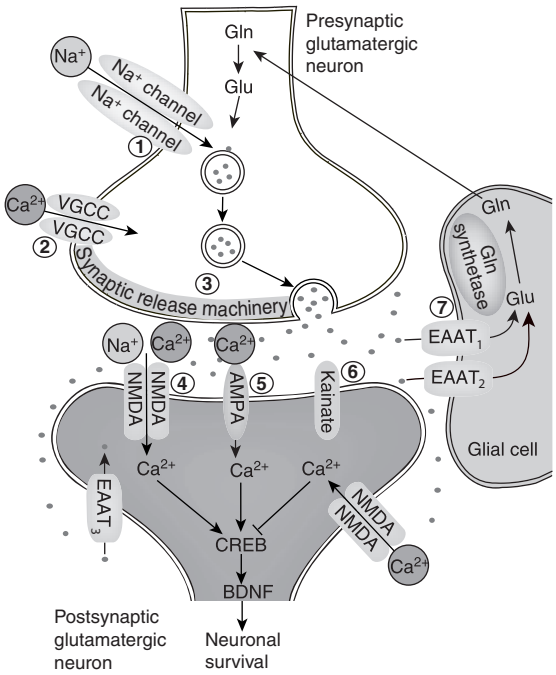

Fig. 2. Schematic representation of a typical glutamatergic synapse, illustrating major functional components discussed in the text and proposed sites of action of riluzole; see text for details and citations. (**1**) Substantial evidence suggests that riluzole may act on the voltage-activated sodium channel, attenuating action potential invasion of the synaptic terminal and thereby reducing glutamate release. (**2**) A few studies suggest that riluzole inhibits voltage-gated calcium channels (VGCC), which may reduce calcium accumulation in the synaptic terminal and likewise reduce glutamate release. (**3**) Indirect evidence, principally the influence of pertussis toxin on the pharmacological effects of riluzole, suggests other modulatory effects on synaptic release of glutamate. (**4**) At high concentrations, riluzole can act directly on the NMDA receptor, the α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor (**5**), and the kainate class of glutamate receptor (**6**); the concentrations at which these effects have been documented *in vitro* are such that they are unlikely to be of relevance *in vivo*. (**7**) Riluzole has recently been found to potentiate uptake of glutamate, perhaps through potentiation of the glial reuptake transporters, excitatory amino acid transporter 1 ($EAAT_1$) and $EAAT_2$. This effect occurs at realistic drug concentrations and may represent the most distinctive pharmacological action of the drug. Dots schematically indicate glutamate molecules. **BDNF** = brain-derived neurotrophic factor; **Ca^{2+}** = calcium ion; **CREB** = cyclic adenosine monophosphate response element binding protein; **Gln** = glutamine; **Glu** = glutamate; **Na^+** = sodium ion.

Riluzole inhibits the release of glutamate *in vivo*[46] and *in vitro*.[47,48,58] This effect may be mediated by blockade of voltage-activated sodium channels.[50-55] Other antiepileptics, such as lamotrigine, also inhibit glutamate release through interaction with voltage-activated sodium channels; this observation raises the question whether riluzole differs from other antiepileptics in pharmacologically meaningful ways. Increasing evidence that riluzole has actions quite distinct from lamotrigine (for example Coderre et al.[76]) suggests that other pharmacological actions, such as those reviewed below (e.g. section 1.1.5), are likely to contribute to its effects.

Riluzole also affects presynaptic calcium dynamics, possibly through several mechanisms. Calcium influx through presynaptic VGCCs is the trigger for neurotransmitter release; therefore, reduction of calcium flux through these channels represents an alternative mechanism whereby a drug can reduce release of glutamate (and of other neurotransmitters). Riluzole has been found to reduce calcium entry through VGCCs.[57] It may do this by direct inhibition of VGCCs;[52,56] alternatively, riluzole may alter presynaptic calcium dynamics through an indirect mechanism, as suggested by the evidence that interference with G-protein-mediated intracellular signalling can attenuate the neuroprotective effects of the drug and its effect on glutamate release.[57-60]

Finally, riluzole has been shown in various systems to interact with voltage-gated potassium channels.[54,61-63,77] These interactions are complex; in some cases riluzole has been reported to reduce potassium channel activation, in other cases to accelerate channel inactivation, and in still others to stabilize the inactivated conformation of the channel. The net contribution of interactions with voltage-activated potassium channels to the reported reduction in presynaptic glutamate release therefore remains unclear.

In conclusion, riluzole has been reported to interact with a large number of ion channels that may contribute to a reduction in glutamate release and thereby to its neuroprotective effects. Differential distribution of voltage-gated channels on different types of axon terminals may explain, in part, how such interactions have specificity for glutamatergic neurotransmission.[49] However, most studies showing riluzole to interact with various ion channels have used concentrations of the drug substantially higher than those that are likely to be achieved *in*

Table I. Pharmacological effects of riluzole that have been characterized in various *in vitro* (and a few *in vivo*) preparations. Most have been described only at unrealistically high riluzole concentrations; the exceptions are the stabilization of the inactive state of the voltage-gated sodium channel and the potentiation of glutamate reuptake

Proposed mechanism	Evidence	Riluzole dose	Reference
Reduced synaptic release of glutamate	Reduced glutamate release from cultured cerebellar granule cells after ibotenic acid stimulation	100 μmol/L (small effect seen at 1 μmol/L)	45
	Reduced glutamate in dialysate from cat striatum; increased potassium-releasable pool of glutamate with long-term treatment	10 μmol/L	46
	Reduced glutamate in superfusate of dissected hippocampal area CA1 after potassium stimulation	10–30 μmol/L	47
	Reduced glutamate release after electrical stimulation of cortical slices	100 μmol/L; EC_{50} = 19.5 μmol/L	48
	Reduced excitatory postsynaptic responses in hippocampal slices	20 μmol/L	49
Blockade of voltage-gated sodium channels	Shifts voltage-inactivation curve of voltage-gated sodium channels at nodes of Ranvier	0.15–100 μmol/L; K_I for stabilizing inactivated sodium channels = 0.29 μmol/L	50
	Reduced voltage-gated sodium currents in *Xenopus* oocytes	Calculated K_I for stabilizing inactivated sodium channels = 0.2 μmol/L	51
	Reduced peak sodium currents in dissociated cortical neurons	EC_{50} = 1 μmol/L	52
	Reduced voltage-gated sodium channels in dorsal root ganglion	~100 μmol/L for resting state; 2–3 μmol/L for inactivated state	53
	Reduced sodium currents in cultured cortical neurons	10–300 μmol/L; calculated IC_{50} = 51 μmol/L	54
	Inhibition of non-inactivating (persistent) sodium current in patch-clamped cultured rat cortical neurons	EC_{50} = 2 μmol/L	55
	Reduction by tetrodotoxin of riluzole-induced postsynaptic responses in hippocampal slice	20 μmol/L	49
Inhibition of VGCCs	Inhibition of VGCCs in dorsal root ganglion	~40 μmol/L	56
	Inhibition of low-voltage activated VGCCs in dissociated cortical neurons	10–30 μmol/L (small effect seen at 1 μmol/L)	52
	Attenuation of riluzole inhibition of stimulated glutamate release from rat synaptosomes by calcium channel antagonists	EC_{50} = 1–2 μmol/L	57
Indirect modulation of calcium channels through a G-protein-mediated process	Glutamate-induced aspartate release from cultured cerebellar granule cells attenuated by pertussis toxin	10 μmol/L	58
	Potentiation from NMDA-induced toxicity attenuated by pertussis toxin	100 μmol/L 10 μmol/L	35 59
	Attenuation of the inhibition of VGCCs by riluzole in dorsal root ganglion by inhibition of G-protein signalling	30 μmol/L	60

Continued next page

Table I. Contd

Proposed mechanism	Evidence	Riluzole dose	Reference
	Blockade by pertussis toxin of the attenuation of glutamate release from synaptosomes by riluzole	1 μmol/L	57
Modulation of potassium channels	Attenuation of late outward current after depolarization of acutely dissociated cortical neurons	88 μmol/L	54
	Stimulation of two background potassium channels	10–100 μmol/L	61
	Slowed inactivation of Kv1.4 channels	IC_{50} = 70 μmol/L	62
	Inhibition of Kv4.3 channels	IC_{50} = 115.6 μmol/L; K_I for inactivated state = 1.2 μmol/L	63
Interactions with postsynaptic glutamate receptors	Functional antagonism of NMDA and non-NMDA receptors in *Xenopus* oocytes	IC_{50} = 18.2 μmol/L (NMDA) IC_{50} = 167 μmol/L (kainate)	64
	Noncompetitive antagonism of AMPA receptors in dissociated cortical cells	IC_{50} = 100 μmol/L	65
	Noncompetitive antagonism of AMPA receptors in spinal cord	IC_{50} = 1.54 μmol/L	66
Increased neurotrophins (likely to be a downstream effect)	Increased levels of BDNF, GDNF and NGF in medium from cultured astrocytes after riluzole treatment	100 μmol/L	67
	Increased BDNF and neurogenesis after systemic injection of riluzole in rats	20 mg/kg	68
Potentiation of glutamate uptake	Potentiated glutamate uptake by spinal cord synaptosomes	0.1–1 μmol/L 1–300 μmol/L	69 70
	Riluzole potentiates glial uptake of glutamate in primary astrocyte cultures	1 μmol/L	71
	Reversal of impaired glutamate transport seen after nerve injury	1–4 mg/kg	72
Increased glutamate synthesis (likely to be a downstream effect)	Increased conversion of glutamine to glutamate, as measured by ^{13}C-MRS	4 mg/kg	73
Modulation of other neurotransmitter systems	Impaired electrically induced neurotransmitter release from mouse neocortical slice		48
	acetylcholine	IC_{50} = 3.3 μmol/L	
	dopamine	IC_{50} = 6.8 μmol/L	
	Increase in depolarizing effect of glycine and GABA	100 μmol/L to 1 mmol/L	74
	Prolonged decay of GABAergic inhibitory postsynaptic currents	10–100 μmol/L	75

^{13}C-MRS = ^{13}C-magnetic resonance spectroscopy; **AMPA** = amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; **BDNF** = brain-derived neurotrophic factor; **EC_{50}** = half maximal effective concentration; **GDNF** = glial-derived neurotrophic factor; **IC_{50}** = half maximal inhibitory concentration; **K_I** = apparent dissociation constant; **NGF** = nerve growth factor; **VGCC** = voltage-gated calcium channel.

vivo (see table I and further discussion in sections 1.1.2–1.1.5).

1.1.2 Glutamate Receptors

Synaptic glutamate binds to a number of ionotropic and metabotropic receptors. The amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors ($GluR_{1–4}$) and kainate receptors ($GluR_{5–7}$ and $KA_{1–2}$) are oligoheteromers that mediate much of the postsynaptic glutamate-induced current under normal conditions. The metabotropic glutamate (mGlu) receptors couple to diverse second messenger pathways and downstream cellular events in diverse ways. Of particular relevance to the current discussion, the type II mGlu receptors ($mGlu_2$ and $mGlu_3$) are present presynaptically and inhibit synaptic release of glutamate;[78] type II mGlu receptors can mediate feedback inhibition of glutamate release, reducing the activity of glutamatergic synaptic terminals when stimulation of the presynaptic autoreceptors reaches a sufficient level.

The NMDA receptors are also heteromeric ionotropic receptors; they exhibit several unique properties that suit them to a variety of regulatory functions. At resting membrane potential, the transmembrane pore of the NMDA receptor is blocked by a magnesium ion; activation of the receptor therefore requires simultaneous binding of glutamate and depolarization of the postsynaptic cell (which expels the divalent magnesium cation from the transmembrane pore and thus unblocks the pore for the passage of other ions). Through this dual gating, the NMDA receptor functions as a coincidence detector, which equips it to play a critical role in the induction of various forms of synaptic plasticity.[79] When activated, the NMDA receptor allows both sodium and calcium to enter the cell; calcium ions can bind to a variety of intracellular proteins, allowing coupling of an electrical event, ion flux through the activated receptor, to intracellular chemical events.

All of these classes of glutamate receptor (AMPA, kainate, mGlu and NMDA receptors) are present in the postsynaptic membrane; however, receptors are also present extrasynaptically, presynaptically and on glial cells. We have already noted the example of class II mGlu receptors being found presynaptically and having a role in feedback inhibition of glutamate release. NMDA receptors are found both synaptically and extrasynaptically, an important fact to which we will return below, and on glial cells.[80]

Riluzole produces a functional antagonism of both NMDA and kainate receptors *in vitro*.[64] More recently, it has been shown to produce noncompetitive antagonism of AMPA receptors in rat spinal cord[66] and cortex.[65] However, riluzole affects these receptors only at rather high concentrations, with the exception of a single study in spinal cord neurons[66] (table I). Riluzole has not been found to interact with any of the known ligand sites on any glutamate receptor. It is unclear to what extent direct interactions with glutamate receptors contribute to the actions of riluzole.[81]

1.1.3 Trophic and Toxic Effects of Glutamate

Synaptic glutamate contributes to neuronal survival, especially through activation of the NMDA receptor.[82-86] Convergent evidence supports a central role for a conserved signalling pathway in the prosurvival effects of glutamate (although many other pathways are likely to contribute). Calcium influx through synaptic NMDA receptors leads to activation of intracellular second messenger signalling cascades (figure 2). These activate transcriptional regulators in the nucleus,[87] such as the cyclic adenosine monophosphate response element binding protein[88] and nuclear factor-κB.[89,90] Under many circumstances, these transcriptional regulators have a net neuroprotective effect,[91,92] in part through stimulation of growth factors such as brain-derived neurotrophic factor (BDNF).[90,93]

Strikingly, riluzole can increase the expression of trophic factors, including BDNF.[67,68] This is likely to be an indirect consequence of its direct effects on glutamatergic neurotransmission, but speaks to how it appears to modulate the balance between trophic and toxic effects of glutamatergic stimulation.

The trophic effect and NMDA receptor stimulation contrasts with the equally well established role of strong glutamatergic activation, and NMDA activation in particular, in excitotoxicity and neuronal death.[94-96] NMDA-mediated excitotoxicity has been proposed to be a major contributor to the progressive neuronal degeneration seen in brain ischaemia,[97] ALS,[98] Alzheimer's disease[99] and other neurodegenerative processes, including, per-

haps, stress-induced neuronal damage in neuropsychiatric conditions such as major depression.[100] The hypothesis that toxic effects of glutamate contribute to neurodegeneration in these conditions motivates the use of antiglutamatergic medications such as memantine[101] and riluzole[10] for these and other degenerative neurological conditions.

Recent data suggest that stimulation of synaptic NMDA receptors activates trophic signalling cascades, whereas activation of extrasynaptic NMDA receptors can inhibit these cascades and contribute to a net toxic effect.[102-104] Synaptic and extrasynaptic receptors are coupled to distinct patterns of downstream activation, with synaptic receptors coordinately upregulating a number of prosurvival genes and downregulating proapoptotic genes, while activation of extrasynaptic receptors induces a chloride channel known to contribute to neuronal death.[105] The distinction between trophic and toxic effects of glutamate stimulation of neurons may therefore derive less from the intensity or duration of activation of NMDA and other glutamate receptors than from the balance of stimulation of synaptic and extrasynaptic receptors. Physiological or pathological events that disrupt this balance, either by reducing synaptic activity or by increasing tonic levels of extrasynaptic glutamate, may therefore have profound effects on neuronal integrity and function (figure 2).

Tonic and phasic levels of glutamate are therefore under tight homeostatic regulation. Modulating this regulation, and thereby potentially normalizing pathological disruptions of glutamate homeostasis, is likely to be a mechanistically important aspect of the pharmacological profile of riluzole.

1.1.4 Glutamate Homeostasis

Extrasynaptic glutamate is present at very low levels. Glutamate levels in the synaptic cleft have been estimated to exceed 1 mmol/L during synaptic transmission.[106] In contrast, tonic glutamate levels in the extracellular space, under normal conditions, are in the 3–4 μmol/L range[42] (although a recent study in slices *in vitro* suggests that it may be even lower[107]).

Synaptic glutamate derives primarily from regulated release from the presynaptic terminal. Synaptic signalling is terminated by removal of glutamate from the synaptic cleft by a number of excitatory amino acid transporters (EAATs).[42,108] Of these, the glial transporters $EAAT_1$ (also known in rodents as GLAST) and $EAAT_2$ (or GLT-1) are most critical in preventing pathological accumulation of glutamate;[109] knockdown of either glial transporter leads to glutamate accumulation and excitotoxicity, while knockdown of the primary neuronal transporter, $EAAT_3$ (or $EAAC_1$) does not.[110,111] Clearance of synaptically released glutamate is directly related to the degree of astrocytic coverage of neurons,[112,113] consistent with this central role of glia in glutamate clearance. Glutamate reuptake – an essential part of the glutamate-glutamine cycle – is energetically costly; consequently, energy deprivation (as during a reduction in perfusion) leads to a rapid decrease in glutamate uptake and hence an accumulation of extrasynaptic glutamate.[114] Experimental inhibition of glial reuptake likewise leads to rapid glutamate accumulation in the extracellular space.[115]

The capacity of local astrocytes to remove glutamate released into the synapse can be dynamically modulated. Glial glutamate transporters are induced *in vitro* after neuronal activity.[116] In an intriguing recent study, Genoud et al.[117] found that repeated sensory stimulation can increase the expression of $EAAT_1$ and $EAAT_2$ 2-fold (while levels of the primary neuronal glutamate transporter, $EAAT_3$/$EAAC_1$, remain unchanged). Furthermore, this same sensory stimulation led to an increased ensheathment of cortical synapses by astrocytes.[117] These changes persisted for 4 days following sensory stimulation, but then resolved. Thus, both the expression of glutamate transporters by astrocytes and their anatomical arrangement relative to the synaptic cleft, which also influences their ability to scavenge glutamate, can be dynamically and reversibly modified by experience. Regulation may also occur at the level of translation rather than of gene expression, as suggested by the ability of several extracellular factors to regulate the translation of $EAAT_2$ in cultured astrocytes.[118]

EAAT function can be further regulated through interacting proteins, including the glutamate transporter-associated proteins (GTRAPs) and a protein known as Ajuba.[119-122] These proteins link EAATs to the actin cytoskeleton and regulate their activity by affecting their localization or insertion into the

neuronal or glial membrane. These proteins may also alter EAAT function via allosteric modulation. For example, overexpression of $GTRAP_{3-18}$ reduces the activity of $EAAT_3$ by reducing its affinity for glutamate.[119] The GTRAPs represent a potentially very flexible and dynamic mechanism whereby EAAT activity may be regulated.

This ready modulation suggests that activity of glial glutamate transporters may represent a therapeutic target. Recent studies have shown that available pharmaceutical agents can regulate EAAT activity.[123] Such upregulation may have therapeutic applications in various neurological and psychiatric conditions.[123,124]

1.1.5 Riluzole Potentiates Glial Glutamate Uptake

A growing body of evidence suggests that normalizing perturbed extrasynaptic glutamate levels might have beneficial effects in many neurological conditions.[125] Potentiation of glial reuptake of glutamate has been identified as a promising therapeutic mechanism in ALS[123] and other conditions.[76,124] Potentiation of glial glutamate uptake may be the most distinctive pharmacological action of riluzole.

In rat synaptosomes (isolated synaptic terminals), acute riluzole treatment was shown to increase glutamate uptake.[69,70] More recently, riluzole was shown to specifically enhance glutamate uptake by astrocytes in culture.[71] The same effect has been documented *in vivo* in rat spinal cord, where riluzole reverses the decrease in glutamate transport seen after nerve injury.[72] These effects are likely to derive from increased expression or activity of the primary glial glutamate transporters, $EAAT_1$ and $EAAT_2$, although the precise mechanisms, including the molecular targets with which riluzole interacts to produce this enhanced glutamate clearance, have yet to be elucidated. *In vivo*, long-term riluzole treatment enhances glutamate synthesis and metabolism,[73] which may result from enhanced glial reuptake and processing.

Riluzole may produce greater reductions in extrasynaptic than synaptic glutamate levels. As described in section 1.1.3, synaptic and extrasynaptic glutamate can have dramatically different effects on a neuron. It is therefore of substantial importance whether the upregulation of glial glutamate reuptake has a greater effect on synaptic or extrasynaptic glutamate levels. Riluzole was found to maximally potentiate glutamate reuptake by cultured astrocytes at a glutamate level of 10 μmol/L, with less percentage enhancement at either lower or higher levels.[71] Extracellular glutamate levels have been estimated to be 3–4 μmol/L, whereas synaptic glutamate can reach levels in excess of 1 mmol/L during synaptic transmission.[42,106] According to these data, therefore, riluzole may potentiate the uptake of extrasynaptic glutamate in some regions, perhaps perisynaptically, where diffusion from the synapse is expected to lead to local glutamate levels in excess of those found further from the synapse, or in regions where extrasynaptic glutamate is pathologically elevated. However, riluzole is likely to have little effect, at least by this mechanism, on synaptic glutamate during transmission. Riluzole may, of course, truncate synaptic transmission by enhancing reuptake in the perisynaptic region; such an effect could contribute to the presynaptically reduced glutamate signalling reported by Prakriya and Menerick.[49]

The possibility that riluzole has a greater effect on extrasynaptic than on synaptic glutamate may help explain the finding that riluzole can induce trophic factors, including BDNF.[67,68] This observation is surprising at first blush, since riluzole is an antiglutamatergic agent and BDNF is known to be stimulated by synaptic glutamate. However, if riluzole preferentially reduces extrasynaptic glutamate and thereby increases the ratio of synaptic to extrasynaptic NMDA stimulation, the net effect may be activation of prosurvival signalling pathways, activation of cyclic adenosine monophosphate response element binding protein and other transcription factors, and synthesis of trophic factors.

Astrocytic glutamate metabolism is closely coupled to brain energy use and therefore to core metabolic processes.[126] Potentiation of this process by riluzole may therefore explain the observation that riluzole can increase brain glucose metabolism, as measured by magnetic resonance spectroscopy (MRS) in rats.[73] This may also explain the recent observation that riluzole treatment increases levels of hippocampal *N*-acetylaspartate (NAA) in patients with generalized anxiety who responded to riluzole therapy.[127] NAA is also coupled to core metabolic processes and may increase in parallel with the

general increase in glucose metabolism observed in animals after riluzole treatment.[73]

Several of the other reported effects of riluzole may, upon re-analysis, be explicable in terms of glutamate reuptake rather than inhibition of synaptic glutamate release. For example, the conclusion that riluzole attenuates glutamate outflow was originally reached from the observation that it reduces extracellular glutamate in cat striatum[46] and in the perfusate of hippocampal slices *in vitro*.[58] In both cases, the observed effect on extracellular glutamate levels is equally well explained by increased astrocytic reuptake of extrasynaptic glutamate.

Riluzole increases glutamate reuptake at concentrations substantially lower than those found to affect ion channels and to affect glutamate release (table I). The maximal effect of this drug on astrocyte uptake of glutamate was found at riluzole concentrations of 1–10 μmol/L; substantially enhanced uptake of 10 μmol/L glutamate was found with concentrations of only 1 μmol/L riluzole.[71] Interactions with the inactivated state of voltage-gated sodium channels have been found at similar concentrations in several studies, but most other effects of riluzole have been described only at much higher concentrations (table I). Effects on glutamate release have been described at 10[46] 20[49] or 100 μmol/L[48] of riluzole (table I). No measurements of intracerebral or CSF riluzole concentrations in patients treated with the standard dose have been published, but peak serum concentrations have been reported to generally fall between 0.2 and 0.8 mg/L (corresponding to approximately 1–4 μmol/L) and trough concentrations between 0.02 and 0.15 mg/L (0.1–0.5 μmol/L).[128] If concentrations in the CNS parallel those measured in serum, the effects documented on astrocytic reuptake of glutamate at riluzole 1 μmol/L may be of greater physiological importance than those on glutamate release documented at higher concentrations.

1.2 Other Neurotransmitters

While the prominence of the effects of riluzole on glutamatergic neurotransmission has been amply documented, the drug has been shown to alter signalling by other neurotransmitters. Therefore, interpretation of its effects solely in terms of modulation of the glutamate system must be made with caution.

In vitro studies of neurotransmitter release in the presence of riluzole confirm the drug's effects on glutamate but have also shown attenuation of release of acetylcholine and dopamine, in both rodent and human neocortex.[48] Riluzole can also directly interact with nicotinic acetylcholine receptors, at least in skeletal muscle.[74] It is noteworthy that all of these effects are seen at riluzole doses that are likely to substantially exceed concentrations achieved in patients (table I).

Riluzole may also interact with inhibitory neurotransmitters, although most findings are again at high drug concentrations. Concentrations of 100 μmol/L to 1 mmol/L can increase the depolarizing effect of GABA and glycine receptor channels, probably through direct interactions with the channel molecules.[75,129] Enhancing GABAergic inhibitory function could provide another mechanism, independent of reduction in glutamate, by which riluzole could reduce neuronal excitability and possibly contribute to neuroprotection. However, effects on GABA function have not been clearly documented at concentrations of riluzole that are likely to be of relevance *in vivo*.

1.3 Functional Overlap with Antidepressants

Although the direct pharmacological targets of riluzole differ from those of conventional antidepressants, some of the documented downstream effects of riluzole treatment overlap with known effects of established antidepressant medications. Such overlapping downstream effects may contribute to the apparent antidepressant effects of riluzole.

For example, long-term antidepressant treatment (both pharmacotherapy and electroconvulsive seizure) have been shown to increase BDNF and other neurotrophic factors;[130,131] BDNF is likewise upregulated by riluzole.[67,68] Long-term antidepressant treatment stimulates hippocampal neurogenesis,[132,133] as does riluzole.[68] Conventional antidepressants modulate the function of AMPA receptors,[134] and direct modulators of AMPA receptor function hold promise as novel antidepressants (reviewed by Witkin et al.[135]); AMPA receptor function[66] and trafficking[136] are likewise modulated by riluzole.

1.4 Summary of the Pharmacological Effects of Riluzole

In conclusion, riluzole has a number of pharmacological actions, including interactions with several types of ion channels, cellular signalling mechanisms, and glutamate reuptake by astrocytes (figure 2). However, many of these actions have only been demonstrated at concentrations of riluzole that are unlikely to be achieved in the brains of patients. The recently documented ability of micromolar concentrations of riluzole to potentiate the reuptake of glutamate by astrocytes is therefore of particular interest. Reduction of extracellular glutamate through potentiation of glial reuptake is likely to be an important therapeutic mechanism in several disorders.[123,124] Further *in vitro* and *in vivo* studies will be required to better elucidate the pharmacological actions of riluzole at concentrations achievable in the brains of patients and to provide greater understanding of how these different mechanisms may contribute to its clinical effects.

2. Riluzole in the Treatment of Neurological Disease

The use of riluzole in ALS has recently been reviewed,[10] and its use has also been explored in other neurodegenerative diseases, albeit with generally disappointing results. Most recently, promising animal data have emerged regarding the use of riluzole in the treatment of neuropathic pain. While it is not our intent to examine the use of riluzole in these neurological conditions comprehensively or critically, a brief review is appropriate to the discussion of the use of riluzole in psychiatric conditions in section 3.

2.1 Amyotrophic Lateral Sclerosis (ALS)

Riluzole remains the only medication approved by the FDA for the treatment of ALS. Double-blind, placebo-controlled trials have suggested a modest but statistically significant increase in survival in riluzole-treated patients relative to placebo-treated controls.[8,9] Subsequent trials have included patients with more advanced disease and have been negative,[137,138] but a recent meta-analysis of all available double-blind data shows a survival benefit.[10] Other studies have examined quality-of-life variables and persistence of mild disease and, again, have generally found a small but significant benefit from riluzole treatment.[139]

The use of riluzole in ALS was motivated by the observation that glutamate homeostasis is perturbed in patients with the disease.[140,141] The inhibition of glutamate release by riluzole has been thought to moderate excessive build-up of synaptic glutamate, thus moderating excitotoxicity.[81] However, as reviewed in section 1.1.3, excess extrasynaptic glutamate may be particularly damaging to neurons, and enhancing glutamate clearance may therefore also be an important component of the therapeutic efficacy of riluzole in ALS. It is for this reason that other potentiators of glutamate uptake are being actively sought as novel treatments for this devastating disease.[123]

2.2 Other Neurodegenerative Diseases

Excitotoxicity through excess or dysregulated glutamate may contribute to other neurodegenerative diseases.[142] The efficacy of riluzole in ALS, presumed to be through a reduction in excitotoxic cell damage, has therefore motivated small trials of the medication in other neurodegenerative disorders. While preclinical data have been promising, the results of clinical studies in other neurodegenerative disorders have, by and large, been disappointing, and riluzole has not been established to have a role in the treatment of any other degenerative neurological condition.

Several trials have explored the use of riluzole as a neuroprotective agent in Parkinson's disease and related disorders (reviewed by LeWitt[143]). Studies *in vitro* and in animal models have suggested that riluzole may protect mesencephalic neurons against oxidative damage and death.[22-25] However, double-blind trials have shown no clinically significant effect on the progression of Parkinson's disease[144] or on dyskinesias in more advanced disease.[145,146] More recently, a placebo-controlled trial of riluzole in multiple system atrophy likewise showed no meaningful reduction of symptoms.[147]

Riluzole therapy is being actively explored in Huntington's disease, again with the hypothesis that it may provide benefit through its neuroprotective effects. As in Parkinson's disease, studies in animal

models suggest a beneficial effect.[26,27] An open-label study in Huntington's disease[148] suggested some symptom reduction at 3 months but no benefit at 1 year. A phase II study[149] of 8 weeks of treatment found a possible reduction in chorea, but no effect on other measures of symptoms or function. A trial of longer-term therapy is ongoing; riluzole may yet prove to have some utility in the treatment of Huntington's disease.

2.3 Neuropathic Pain

Dysregulation of glutamate has been proposed to contribute to neuropathic pain. Specifically, glutamate transporter expression and activity were found to be altered after nerve injury and to contribute to neuropathic pain in rats; postoperative riluzole could considerably reduce behavioural manifestations of allodynia.[72] More recently, this effect was replicated and riluzole was found to be substantially more effective in modulating neuropathic pain than gabapentin or lamotrigine.[76] Notably, lamotrigine shares with riluzole the inhibitory effect on voltage-gated sodium channels, but lamotrigine does not potentiate glutamate reuptake. Lamotrigine was not found to reduce extrasynaptic glutamate levels in this study, suggesting that the potentiation of astrocytic reuptake, rather than any reduction of glutamate release, explains the effect of riluzole on extrasynaptic glutamate.

Despite these promising recent results in animal models, the single study of riluzole in the treatment of neuropathic pain in human patients that has been published to date showed no benefit.[150] It remains unclear whether the finding of dysregulated glutamate after nerve injury generalizes to humans, and whether riluzole will prove to be of use in some cases of neuropathic pain.

2.4 Antiepileptic Properties

As noted in section 1, riluzole was originally described as an antiepileptic drug; in animal models, it was able to prevent convulsions caused by either electroshock or inhibitors of GABA biosynthesis.[21] Further studies in animal models have likewise shown its potential as a primary or adjunctive antiepileptic medication.[151-153] One recent study in rats found efficacy superior to that of valproic acid in seizure prevention.[154] However, to date no clinical studies of riluzole as an antiepileptic medication have been described.

3. Riluzole in the Treatment of Psychiatric Disease

Recent studies have implicated glutamate dysregulation in the pathophysiology of several psychiatric diseases.[4-7] Therefore, agents that can modulate glutamate have garnered interest in the treatment of a number of conditions. Both monotherapy and pharmacological augmentation with riluzole have been attempted in patients with depression, OCD, GAD, schizophrenia and a variety of other conditions. While definitive double-blind, placebo-controlled data are not yet available for any of these conditions, early results suggest that riluzole may be a useful addition to the psychiatric pharmacopoeia.

3.1 Unipolar Depression

Substantial evidence suggests that glutamate is dysregulated in major depressive disorder.[5,155,156] Some of the strongest evidence for this idea derives from MRS studies that measure *in vivo* levels of glutamate, or of a composite measure known as Glx that combines measures of glutamate and related compounds such as glutamine, in various brain regions. Glx is reduced in the frontal cortex in patients with major depression.[157,158] There may be some regional variation as other studies have found elevated Glx in the occipital lobe in patients with major depression.[43,159] The specifics of such regional variation remain to be elucidated. Regardless, given the intimate relationship between astrocytes and glutamate cycling and homeostasis, disruption of normal glutamate and glutamine levels and metabolism is consistent with the post-mortem observation that glial cells are reduced in number in the frontal cortex of patients with major depression.[160-164] Chronic stress reduces glial proliferation in experimental animals;[165] and experimentally-induced glial loss in the medial prefrontal cortex is sufficient to produce depression-like behaviors, similar to those produced by stress.[166]

Such evidence for glutamatergic dysfunction in major depression motivated the suggestion that glutamate-modulating agents, including riluzole,

might have therapeutic potential.[167,168] Indeed, long-term administration of riluzole has recently been shown to have antidepressant-like effects in the forced swim test, a widely used screening test for antidepressants, and the sucrose preference test, an assay of anhedonia.[169] A first clinical case report, describing a patient with treatment-refractory major depression and OCD, described such an antidepressant effect with riluzole augmentation therapy.[15]

Zarate et al.[11] described riluzole monotherapy in 19 patients with major depressive disorder, most of whom had not responded to several previous efforts at treatment (table II). Riluzole was administered at a dosage of 100–200 mg/day, with 84% of patients taking a dosage higher than the usual ALS therapeutic dosage of 100 mg/day. Thirteen patients (68%) completed the trial. Analysis of all patients showed a statistically significant (33%) improvement in the Montgomery-Åsberg Depression Rating Scale (MADRS)[170] score by week 6; among trial completers, the improvement was 46%. Notably, patients also exhibited a statistically significant decline in anxiety, with a 29% drop in score on the Hamilton Anxiety Rating Scale (HAM-A).[171]

Sanacora et al.[12,13] described the use of riluzole, at a fixed dosage of 50 mg twice daily, as augmentation therapy for major depression with significant residual symptoms despite standard pharmacotherapy; their patients had significantly more severe depression and a substantially larger number of past failed therapeutic trials than those described by Zarate et al.[11] They treated 13 patients, of whom 10 completed at least 6 weeks of treatment. Patients exhibited a statistically significant improvement in depressive symptoms, with a 36% drop in the Hamilton Depression Rating Scale (HAM-D)[173] among those patients who completed 6 weeks of treatment. Strikingly, the greatest improvement among responders was seen in the first 2 weeks of treatment, and the beneficial effect on depressive symptoms was statistically significant after a single week of treatment. The beneficial effect of riluzole treatment remained statistically significant for 3 months of follow-up. As in the study of Zarate et al.,[11] a statistically significant improvement in anxiety symptoms was also seen, with the HAM-A score improving by 31% among those patients who completed 6 weeks of treatment.

Statistically significant improvement in depression has also been reported in conjunction with open-label trials of riluzole in GAD[19] and OCD,[16] which are discussed further in sections 3.3 and 3.4, respectively.

These studies were small, open-label trials lacking a control group; therefore, they must be interpreted with caution. Double-blind, placebo-controlled trials are necessary to confirm these early results. However, in both trials, most of the patients had failed to respond to multiple previous attempts at pharmacotherapy.[11,13] Therefore, the benefit seen over a relatively short period with riluzole monotherapy or augmentation is encouraging. Especially in light of other evidence of the benefit of glutamate modulators in the treatment of depression,[176] these early data suggest that riluzole may represent an important new option in the treatment of major depression.

3.2 Bipolar Depression

Patients with bipolar affective disorder spend 95% of their symptomatic episodes in the depressed state. However, the evidence base guiding pharmacotherapy of bipolar depression is limited[177] and many clinicians are reluctant to aggressively use standard antidepressants in these patients because of the concern that they will trigger a manic or mixed state.[178] Therefore, new therapeutic options are urgently needed. Evidence from MRS studies in bipolar disorder suggests an increase in glutamate and related metabolites (Glx) in several cortical regions, independent of mood state.[179] This finding, together with the evidence suggesting efficacy of riluzole in the treatment of major depression, has motivated exploration of the use of the agent in bipolar depression.

Zarate et al.[14] treated 14 patients with bipolar depression with a combination of lithium and riluzole for 8 weeks; 57% of patients completed this trial. All patients were treated with lithium for a minimum of 4 weeks before starting riluzole. Riluzole was administered at a dosage of 100–200 mg/day; 79% of patients received a dosage higher than the usual ALS dosage of 100 mg/day, with the average dosage being 171.4 mg/day. Statistically significant improvement on the MADRS[170] was observed by week 5, with a 60% overall reduc-

Table II. Open-label studies in treatment-refractory populations have suggested that riluzole may have therapeutic efficacy in unipolar and bipolar depression, generalized anxiety disorder and obsessive-compulsive disorder. Placebo-controlled studies are needed to validate these promising open-label results

Disorder	Type of therapy	Dosage (mg/day)	Patients [completers]	Primary outcome	Duration (wk)	Outcome (completers)	Reference
Major depressive disorder	Monotherapy	169 ± 27.2	19 (9M, 10F) [13]	MADRS	6	46% decline in MADRS (32% responders, 21% remitters) 29% decline in HAM-A	11
Major depressive disorder	Augmentation	100	13 (6M, 7F) [10]	HAM-D	6	36% decline in HAM-D (40% responders, 30% remitters) 31% decline in HAM-A	13
Bipolar depression	Augmentation of lithium	171 ± 42.6	14 (10M, 4F) [8]	MADRS	8	60% decline in MADRS (50% responders, 50% remitters) No change in YMRS	14
Generalized anxiety disorder	Monotherapy	100	18 [15]	HAM-A	8	62% decline in HAM-A (80% responders, 53% remitters) 37% decline in ASI	19
Obsessive-compulsive disorder	Augmentation	100	13[a] [6 completers at 12 wk]	Y-BOCS	12[a]	42% decline in Y-BOCS (five responders) 34% decline in HAM-D 34% decline in HAM-A	16
Obsessive compulsive disorder	Augmentation	100–200	6 [6]	CY-BOCS	12	39% decline in CY-BOCS (four responders)	18

a This study was begun as a 6-week study but was extended midway because of the observation that clinical improvement continued after week 6. Three patients were treated for 6 weeks, four for 10 weeks and six for 12 weeks. One patient withdrew at week 9 because of a family emergency.

ASI = Anxiety Sensitivity Index; **CY-BOCS** = Children's Yale-Brown Obsessive-Compulsive Scale;[172] **F** = female; **HAM-A** = Hamilton Anxiety Rating Scale;[171] **HAM-D** = Hamilton Depression Rating Scale;[173] **M** = male; **MADRS** = Montgomery-Åsberg Depression Rating Scale;[170] **Y-BOCS** = Yale-Brown Obsessive-Compulsive Scale;[174] **YMRS** = Young Mania Rating Scale.[175]

tion in MADRS score across the 8 weeks of treatment. There was no effect on scores of mania and no case of emergent hypomania or mania after the initiation of riluzole treatment.

As in the case of the two studies published for major depressive disorder, this uncontrolled, open-label study must be interpreted with caution and requires replication in a double-blind, placebo-controlled design. However, it provides promising evidence that riluzole may prove efficacious in the treatment of bipolar depression.

3.3 Generalized Anxiety Disorder

Anxiety disorders are often co-morbid with depression; aspects of their pathophysiology may overlap. This is suggested, for example, by the utility of SSRIs in the treatment of both major depression and of several anxiety disorders. Anxiety disorders are most often thought of in association with dysfunction of GABAergic inhibitory neurotransmission, as exemplified by the efficacy of GABAergic medications such as benzodiazepines. However, it has been suggested that glutamate dysregulation may also make an important contribution to anxiety states.[7] As noted in section 3.1, anxiety ratings were found to improve in the depressed patients treated with riluzole monotherapy[11] or augmentation therapy.[13,16]

Mathew et al.[19] treated 18 GAD patients with riluzole monotherapy, at a fixed dosage of 50 mg twice daily. Fifteen patients completed an 8-week open-label trial period. HAM-A scores declined by 62% overall; 12 of the completers responded to the riluzole treatment and 8 reached remission. HAM-D scores also improved to a statistically significant extent over the course of the 8-week trial. Patients who had co-morbid panic disorder also responded to riluzole monotherapy; five of seven patients with co-morbid panic disorder completed the study; all of them experienced reduced panic symptoms, and three remitted.

Coupled with evidence from studies in depression and OCD that riluzole can have anti-anxiety effects in other populations, this finding in GAD suggests that this and other glutamatergic agents may come to have an important role in the treatment of pathological anxiety.

3.4 Obsessive-Compulsive Disorder

Glutamate dysregulation has been implicated in the pathophysiology of OCD.[16,180,181] Fewer MRS data are available than in the case of affective disorder; however, MRS examinations of a small number of patients suggest altered levels of glutamate and related compounds (Glx) in the striatum, with variable perturbations in the cortex.[180,181] Further evidence for glutamatergic perturbation in OCD derives from the finding of elevated CSF glutamate levels in patients with OCD relative to healthy controls[182] and the recent association of mutations in the gene for $EAAT_3/EAAC_1$, the primary neuronal glutamate reuptake transporter, with cases of early-onset OCD.[183-185]

Coric et al.[16] treated 13 patients with profoundly treatment-refractory OCD with riluzole augmentation therapy at a dosage of 50 mg twice daily for 6–12 weeks. OCD symptoms, as measured by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS),[174] declined by a statistically significant 42% overall ($p < 0.001$). Seven patients exhibited a >35% reduction in Y-BOCS, and five of these patients had a reduction of Y-BOCS score out of the severe range, qualifying them as treatment responders by stringent criteria. Statistically significant improvements in depression (measured by HAM-D) and anxiety (measured by HAM-A) were also observed.

A clinical case series of an additional 13 patients with OCD who were treated with riluzole and who have been followed at our centre since the completion of the initial open-label study produced similar results.[17] Six of 13 patients treated clinically with riluzole 100–200 mg/day showed a 35% or greater reduction in Y-BOCS by week 12 of the treatment. Several patients have continued to take the drug for over a year, while being followed continuously at our clinic; in most patients, initial response has been maintained and riluzole has been well tolerated. As in the published open-label study,[17] a substantial effect of riluzole augmentation on co-morbid depressive symptoms has been observed.

Preliminary data also suggest efficacy in treatment-refractory OCD in the paediatric population. A 12-week, open-label study of riluzole in six patients

with paediatric OCD was recently completed at the National Institute of Mental Health. This study demonstrated a 39% improvement in the Child Y-BOCS scores (CY-BOCS) for the entire group of six patients, with four showing clinically meaningful improvement.[18]

OCD can be described along several symptom dimensions, which may represent distinct (although overlapping) syndromes of illness.[186] Of these, compulsive hoarding has proven to be particularly resistant to established pharmacotherapies and to psychotherapy; hoarding may represent an aetiologically distinct entity.[187,188] It is therefore noteworthy that several of the patients described to have had a favourable response to riluzole have had prominent hoarding symptoms. Two of the seven responders in the initial open-label study[16] and several patients treated clinically since then[17,189] had prominent hoarding symptoms. Although many more patients will need to be treated and rigorously evaluated before any definitive conclusions can be drawn, these observations engender optimism that glutamate-based treatments for OCD will provide new treatment options for this difficult-to-treat subpopulation.

3.5 Compulsive-Impulsive Spectrum Disorders

Other compulsive and impulsive disorders, including trichotillomania, impulse regulation disorders such as intermittent explosive disorder, and other entities such as eating disorders and body dysmorphic disorder (BDD), are phenomenologically similar to OCD and may be aetiologically related.[190] Some of these disorders, such as BDD, are often co-morbid with OCD,[191] and serotonergic medications are often of use in other disorders in this cluster. If glutamatergic medications such as riluzole prove to be of use in OCD, it will therefore be of interest to explore their utility in the treatment of other related disorders. While no large studies have explored this area to date, several case reports have suggested the possible utility of riluzole in the treatment of other impulsive-compulsive disorders.

Self-injurious behaviour (SIB) is most frequently associated with borderline personality disorder and presents a difficult clinical challenge.[192] No validated pharmacological approaches exist for treating repeated SIB, although specialized psychotherapies are of proven efficacy and treatment of co-morbid conditions such as depression can help. Pittenger et al.[193] treated two patients with borderline personality disorder, treatment-refractory depression and problematic SIB with riluzole, attempting to target their depressive symptoms. Urges towards SIB and also manifest SIB improved markedly in both patients, although depressive symptoms improved in only one patient.

Trichotillomania is classified as an impulse control disorder; patients exhibit compulsive hair-pulling, which is often experienced as alleviating internal tension. It is difficult to treat pharmacologically; specialized behavioural therapies are effective but are available only in a research setting.[194] Trichotillomania is frequently co-morbid with OCD. Coric et al.[195] treated a patient with life-long, severely impairing, treatment-refractory trichotillomania with riluzole, initially at 100 mg/day and then at 200 mg/day. Hair-pulling improved dramatically over the course of several weeks – the patient's score on the Massachusetts General Hospital Hairpulling Scale[196] declined from 17 at baseline, indicative of severe chronic hair-pulling, to zero. Depression also improved; HAM-D score fell from 26 to 7. This patient continues to do well and to be free of urges to pull her hair 3 years after the initiation of riluzole therapy (Pittenger C and Coric V, unpublished observations).

Pathological skin picking bears a phenomenological resemblance to trichotillomania or to BDD; skin is excoriated in response to an internal urge or a perceived imperfection, often to the point of infection and often with an accompanying internal sense of relief. Sasso et al.[189] described a patient with OCD and depression who also had a life-long history of pathological skin picking, which was sufficiently severe that it had led to several facial skin infections. When riluzole was added to the patient's medication regimen, OCD, depression and pathological skin picking all improved markedly. In addition, the patient's life-long pattern of disordered eating (characterized by restriction and binging/purging behaviours as well as ruminative preoccupation over food intake) improved.

The literature on the use of riluzole in these disorders of the compulsive-impulsive spectrum is limited to a handful of case reports; generalization

and mechanistic extrapolation would therefore be premature. However, the growing collection of reported positive results suggests that the efficacy of the medication extends beyond depression and anxiety. If validated by more extensive observations and, ultimately, by larger appropriately controlled studies, riluzole may prove to be an important adjunct to the treatment of a number of disorders for which little validated pharmacotherapy exists.

4. Tolerability and Adverse Effects of Riluzole

Since riluzole was approved by the FDA for the treatment of ALS in 1996, a substantial literature exists on its tolerability and adverse effect profile. This literature has recently been reviewed, with the general conclusion that the agent is rather well tolerated.[10,197] A potentially significant adverse effect is its effect on the liver; modest and asymptomatic elevation of transaminases is a common, although usually transient, effect.

4.1 Common Adverse Effects in the ALS Population

In the large ALS literature, the most commonly reported adverse effects of riluzole treatment are nausea and asthenia; both were significantly more common in patients treated with riluzole than in placebo-treated subjects in a meta-analysis of double-blind studies.[10] In the two initial large, double-blind trials of riluzole in ALS, asthenia was experienced by 18% of patients receiving riluzole (as opposed to 12% of those receiving placebo) and nausea was experienced by 14% (as opposed to 9% of controls). Other adverse effects occurred with comparable frequency in the riluzole and placebo groups. Overall, 91% of patients receiving riluzole and 90% of controls experienced an adverse effect during these trials.[197] This high incidence of adverse effects reflects the morbidity in the ALS population and is unlikely to generalize to more medically healthy patients with psychiatric disease. On the other hand, patients with ALS typically take riluzole for a relatively brief period of time, because of the progressive natural history of the disease. If riluzole is proven efficacious for psychiatric diseases, such as major depression and OCD, some patients may take it for years. Ongoing monitoring for potential consequences of such long-term therapy will be essential, as it is for any medication.

Vomiting, diarrhoea, anorexia and dizziness were also more frequent in treated patients than in controls in ALS studies, but the difference between groups did not reach statistical significance.[10] A few patients in one study[9] reported perioral paraesthesias; this effect was more common at the 200 mg/day dosage. Perioral paraesthesias have not been reported in other studies.

During an open-label extension follow-up to the initial double-blind studies,[198] a large percentage of patients (88%) continued to report adverse events; however, again, this high percentage is likely to reflect the severe neurological disease and co-morbid medical illness in this population. Of the 516 patients in this follow-up study, 6.2% discontinued treatment as a result of adverse effects. The incidence of asthenia and nausea was 5.4% and 7.2%, respectively.[197,198] Similar modest incidences of nausea and asthenia were observed in a worldwide study of 7916 patients treated with riluzole while the drug was going through the approval process.[197] Because of the absence of a placebo control group in this follow-up population, it is impossible to determine what fraction of these adverse events was attributable to riluzole therapy.

A similar pattern of adverse effects was seen in a double-blind trial of riluzole in the treatment of Huntington's disease.[149] Muscle weakness and dizziness occurred with low frequency, but at a higher rate in the riluzole-treated group than in controls. Other adverse effects were of similar frequency in riluzole-treated patients and controls.

There is a weak association between riluzole dose and the incidence of these minor adverse effects. In the large trial in ALS patients in which dosages of 100, 150 and 200 mg/day were used,[9] and in the trial in Huntington's disease patients in which dosages of 100 and 200 mg/day were used,[149] both mild and moderate to severe adverse effects occurred with greater frequency in the groups receiving the higher dosage.

Overall, the common adverse effects of riluzole compare reasonably well with those of first-line pharmacological treatments for mood and anxiety disorders, such as the SSRIs. Medically significant

adverse effects, such as the metabolic syndrome associated with atypical antipsychotic use, have not commonly been seen with riluzole, although ongoing vigilance is, of course, a requisite if the agent comes to be more frequently used in various clinical populations.

4.2 Transaminase Abnormalities in the ALS Population

Riluzole can lead to reversible transaminase elevations. In the large, double-blind trials of riluzole therapy in ALS,[8,9] elevations of ALT and AST to 3–5 times the upper limit of normal (ULN) were seen in 9% and 5% of patients and elevations to >5 × ULN in 4% and 1% of patients, respectively. Liver function tests (LFTs) normalized within 2 months after discontinuation of riluzole, or after 2–6 months of continuous treatment in patients with elevations of <5 × ULN. Three cases of clinically significant liver pathology have been reported; in all three cases, symptoms resolved upon discontinuation of riluzole treatment.[199,200]

LFT elevations are most likely to occur early in riluzole therapy, although they can occur after extended treatment. Because of the risk of hepatic involvement, it has been suggested that LFT monitoring be performed at baseline and then monthly for the first 3 months of therapy, then quarterly for the balance of the first year, and periodically for the remainder of treatment.[201] Modest elevations should trigger more frequent monitoring; it has been suggested that treatment be discontinued if transaminases are elevated above 5 × ULN.[201] Riluzole treatment is contraindicated in patients with elevated transaminases (>3 × normal) or active hepatic disease; patients with modestly elevated baseline transaminases can be treated with caution and close monitoring, although compromised liver function can lead to decreased clearance of the drug.[197]

4.3 Rare Adverse Effects

Other rare, potentially serious adverse effects have been reported in conjunction with riluzole use in the ALS population, but in all cases they did not emerge during the large controlled trials, and their relationship to the drug (as opposed to progression of the underlying diseases or to unrelated events) remains unclear. Reports of myasthenia, pancreatitis, renal tube impairment, hypertension, methaemoglobinaemia, neutropenia and granulocytopenia have appeared in the literature (reviewed by Bensimon and Doble[197]). Intentional riluzole overdoses have been reported. In one case report, a massive overdose resulted in methaemoglobinaemia, which resolved with supportive treatment.[202] Two cases of amnesia following large riluzole overdoses (30–50 times the normal daily dose) have been reported in patients with Huntington's disease; in one case, the amnesia resolved over several months, but in the other case it persisted for over a year.[203,204] Given that such large overdoses are extremely rare and occur on a background of pre-existing neurological disease, it is difficult to predict what the consequences of overdose in any particular patient might be, and vigilance is warranted.

4.4 Adverse Effects in the Psychiatric Population

The total number of patients who have been described in the six trials summarized in table II remains small, and no double-blind studies have been described to date. Therefore, it is difficult to generalize about the incidence of adverse effects in the psychiatric population, as opposed to the severely ill neurological populations in which a more extensive literature exists. However, it may be that the pattern of adverse effects in psychiatric patients in general will differ from that in patients with ALS or Huntington's disease (the two neurological conditions in which the largest number of patients have been treated), because the underlying brain pathology, independent of riluzole treatment, is quite different. Some adverse effects, which may derive in the ALS population from an interaction of the drug with a diseased nervous system, may prove to be less frequent in a more medically healthy psychiatric population; however, any firm conclusions on this topic will have to await reports of treatment of larger numbers of patients.

In the six open-label studies published to date,[11,13,14,16,18,19] a total of 83 patients have been described. The most common adverse effects reported have been nausea (17%; 14 patients), fatigue or drowsiness (13%; 11 patients), headache (13%; 11 patients) and dry mouth (13%; 11 patients). Less

common adverse effects included dizziness (1 patient), cognitive slowing (1 patient), internal tension (5 patients), abdominal pain (1 patient), diarrhoea (3 patients), weight loss (3 patients), constipation (6 patients), blurred vision (3 patients), and visual illusions (1 patient). Reporting of adverse effects differed across studies, making it difficult to make any statements about the absolute frequency of any of these adverse effects in this population. Furthermore, the absence of a placebo control group in any of these studies renders it impossible to determine what fraction of the reported adverse effects is attributable to riluzole treatment. Overall, the prominence of nausea and fatigue (which has been reported as asthenia in the ALS literature) suggests a similar pattern of adverse effects to that attributable to riluzole in studies of ALS. Most adverse effects, including nausea, headache, and fatigue, improve over the course of a few weeks in most patients (Coric V and Pittenger C, unpublished observations).

Notably, no cases of emergent mania or hypomania after initiation of riluzole treatment (in conjunction with lithium) have been reported.[14]

All six studies monitored LFTs closely; the incidence of ALT elevation varied across reports. Patients with elevated baseline transaminases or known liver disease were excluded from all studies. A total of ten patients (12%) had elevations of at least one liver function measure. One inpatient had a 9-fold elevation in ALT; treatment was continued with increased frequency of monitoring as the patient had experienced a robust treatment response, and ALT fell to 4 × ULN 1 week later and 2 × ULN 2 weeks later, with no symptoms of liver disease.[16]

4.5 Drug Interactions

Three of the published reports describe augmentation studies, in which riluzole was added to the patients' established stable medication regimen,[13,16,18] two describe riluzole monotherapy[11,19] and one describes the use of riluzole in conjunction with lithium.[14] In the three augmentation trials, describing a total of 32 patients,[13,16,18] riluzole was used in combination with a number of different medications, although the total number of patients receiving any particular combination remains very small. Reported studies describe its use in conjunction with SSRIs (fluvoxamine, escitalopram, fluoxetine), tricyclics (clomipramine, imipramine, desipramine), typical and atypical antipsychotics (trifluoperazine, risperidone, quetiapine, aripiprazole), an MAOI (tranylcypromine), bupropion, trazodone, modafinil, atomoxetine, amfetamine mixed salts (Adderall®) and benzodiazepines. No clear association between any particular medication combination and clinical response was evident in any study, although the power to detect such an association remains very small because of the limited number of patients described.

One patient treated in the trial of Sanacora et al.[13] had a good initial response of her depressive symptoms after starting riluzole augmentation, but developed visual distortions and illusions shortly thereafter. These appeared to derive from the unusual combination of riluzole, memantine and bupropion; they resolved when riluzole was continued and these other medications were tapered. This patient had a history of visual distortions on other medication combinations in the past, suggesting a peculiar susceptibility rather than a general phenomenon. Nevertheless, the case highlights the unanticipated adverse effects that may emerge from the addition of riluzole, or any novel agent, to a complex medication regimen.[181]

5. Dosage Considerations

Riluzole is normally given at a dosage of 50 mg twice daily. A dose-finding study in ALS[9] suggested that a lower dosage of 50 mg daily had reduced efficacy, while a higher dosage of 100 mg twice daily had a higher incidence of adverse effects, with little evidence for improved symptomatic control.

There is insufficient published data to formulate recommendations as to the appropriate dosage in the psychiatric population. Several of the published open-label studies[13,16,19] have used a fixed dosage of 50 mg twice daily, while others have used flexible dosing, with many patients receiving up to 100 mg twice daily.[11,14] A higher incidence of adverse effects and a larger number of patients withdrawing from treatment have been reported with the higher dosages.[11,14] However, variation between reporting of adverse effects and triggers for patient withdrawals from the different studies make this observation difficult to interpret. Likewise, in the absence of

placebo control groups and adequate statistical power, the efficacy of a higher dose relative to the standard dose is impossible to determine. In the two trials using riluzole to treat major depressive disorder, a higher dosage (100 mg twice daily)[11] appeared to produce a higher response rate than a lower dosage (50 mg twice daily);[13] however, other differences between the trials and study populations make this observation difficult to interpret (i.e. Zarate et al.[11] used riluzole monotherapy in a less refractory population, while Sanacora et al.[13] used riluzole augmentation in a profoundly treatment-refractory population). Until larger, controlled studies are performed, the decision as to whether to increase the dosage above the standard of 50 mg twice daily will remain one of clinical judgment in individual cases.

6. Cost Considerations

A month's supply of riluzole, at the standard dosage of 50 mg twice daily, can cost $US880.00 (2008 costings) or more at retailers in the US. Therefore, even in patients for whom a brief trial has suggested efficacy, economic considerations can limit therapy. If the benefit of riluzole therapy is substantiated in rigorous trials, the exploration of ways to make it more affordable or of other agents with similar mechanisms of action will be essential in making treatment accessible to the large number of patients who might benefit from a mechanistically novel antidepressant and antianxiety agent.

Riluzole was granted an extended patent because of its orphan drug status; its patent expires in 2013 (Sanofi-Aventis US 020599 001 Dec 12, 1995, RX 5,527814). Therefore, it is likely to remain costly for several years. However, if double-blind studies over the next several years support efficacy in mood and anxiety disorders, the drug may become less costly a few years thereafter.

7. Summary and Conclusion

Glutamate dysregulation has been implicated in the pathophysiology of a number of different psychiatric disorders.[4-7] Agents that seek to normalize this dysregulation may provide benefit to some of the large number of patients who are inadequately treated by existing pharmacological strategies.

Riluzole is antiglutamatergic and neuroprotective. Its mechanism of action has been thought to derive from its inhibition of voltage-gated sodium and calcium conductances, which results in a reduction of the synaptic release of glutamate. More recently, it has been shown to potentiate glial reuptake of glutamate.[71] Several considerations suggest that this latter mechanism, which (unlike many other mechanisms documented *in vitro*) occurs at physiologically realistic drug concentrations, may be of particular importance in the treatment of psychiatric disease.

A particularly intriguing observation is that riluzole maximally potentiates glial reuptake of glutamate at glutamate levels slightly higher that those normally found in the extrasynaptic space.[71] It may be that the drug is particularly effective at reducing extrasynaptic glutamate in regions where it is pathologically elevated and/or where the mechanisms of normal glutamate clearance are impaired, but has relatively little impact on regions in which glutamate homeostasis is operating normally. However, this speculation is based on a single published observation made on cultured astrocytes *in vitro*, at a single dose of riluzole; replication of the effect in less reduced systems is necessary to explore it further.

Open-label studies have recently explored the use of riluzole, either as monotherapy or as augmentation therapy, in a number of neuropsychiatric conditions in which glutamate dysregulation has been implicated. Promising early results have been reported in major depressive disorder,[11,13] bipolar depression,[14] GAD[19] and OCD.[16,18] A number of case reports suggest that its efficacy may extend to other disorders of the compulsive-impulsive spectrum, although more rigorous exploration of such applications is essential. The drug has proven to be quite well tolerated, with discontinuation because of adverse effects being rare in published trials. Asymptomatic elevation of transaminases is common, but typically transient. Baseline and periodic monitoring of liver function tests is requisite.

It is striking that the evidence to date suggests that riluzole may have therapeutic utility in a broad range of mood and anxiety disorders – what might be described as the panacea phenomenon. This might reasonably engender scepticism as to whether

the observations of efficacy in multiple disorders will be confirmed in larger, more rigorous studies. However, other medications, far more intensively studied than riluzole, show similar efficacy in a broad range of neuropsychiatric conditions; for example, SSRIs are used in multiple mood and anxiety disorders, and atypical antipsychotics have been used for their antipsychotic, antianxiety, mood stabilizing and antidepressive properties. Therefore, preliminary evidence of efficacy in disparate conditions does not constitute a reason to assume the results will not be validated upon further study. It may be that glutamate-modulating agents will similarly prove to have efficacy that cuts across conventional diagnostic categories.

All published data on the use of riluzole in psychiatric disease are in the form of uncontrolled, open-label trials or case reports. Validation of these preliminary findings in more rigorously controlled study designs is essential. However, if substantiated in such trials, the combination of a novel (if incompletely understood) mechanism of action, apparent efficacy against depressive, anxiety and obsessive-compulsive symptoms, and a relatively benign adverse effect profile may make riluzole an attractive addition to the psychiatrist's treatment armamentarium.

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