

# Unexpected improvement

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For 30 years, Ms. U, age 53, has experienced treatment-resistant schizophrenia. After she is treated for a neurologic disorder, her psychotic symptoms improve markedly. What could be the cause?

## CASE Relapsing psychosis

Ms. U, age 53, was diagnosed with paranoid schizophrenia at age 21 and has a continuous pattern of frequent relapses and inpatient admissions. She has received therapeutic doses of trifluoperazine, sertindole, haloperidol, loxapine, thioridazine, olanzapine, risperidone, clozapine, and several other antipsychotics not available in the United States. Clozapine had been prescribed at 600 mg/d (average blood level was 350 ng/mL), at times in combination with other antipsychotics or lithium.

Despite treatment, Ms. U has never achieved clinical stability. She has fluctuating yet persistent auditory hallucinations (eg, voices threatening to “announce disasters” or songs of a religious nature), associated disorganized behavior (eg, covering her ears or asking third parties “to turn off the radio”), severe hyponatremia secondary to potomania, paranoid ideation (eg, being followed by a “hidden camera”), and a strong tendency toward negativism, mutism, and emotional lability secondary to her psychotic symptoms. Her affect is predominantly poor and flattened, with very poor insight. Her symptoms are associated with progressive social isolation and poor grooming. Because of her worsening status, Ms. U was admitted to a residential facility 3 years ago.

Ms. U is single and the eldest of 2 siblings. Her parents are deceased; one parent may

have committed suicide. She reports a family history of psychosis in her first cousins, but no history of hereditary neurologic disorders. Ms. U is a heavy smoker, did not complete college, and has a job in a family business.

## The authors' observations

Historically, the prevailing theory to explain the pathophysiology of schizophrenia has been the dopamine hypothesis, which links a hyperdopaminergic state in the mesolimbic system with acute psychosis. This theory could explain positive symptoms of schizophrenia but not other core domains, such as negative symptoms and cognitive dysfunction.<sup>1-3</sup> The glutamate hypothesis postulates a hypoglutamatergic state can be the cause, at least in part, of various symptoms of psychosis, similar to those induced by phencyclidine and ketamine. Antagonists at the glycine modulatory site of the *N*-methyl-D-aspartate (NMDA) receptor are being studied as a way to influence this pathway,<sup>1</sup> which is believed to be influenced by genetic factors.<sup>4</sup>

Glutamate, an amino acid, is the primary excitatory neurotransmitter in the brain. Its action is exerted in 2 types of receptors

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## Clinical Point

ALS affects the corticospinal tracts and anterior horn of the spinal cord, leading to dysfunction of the upper and lower motor neurons

on the postsynaptic neuron: ionotropic and metabotropic.

The activation of NMDA receptors generated by glutamate and glycine coagonist can stimulate an uncontrolled release of calcium and subsequent cell death known as excitotoxicity. This phenomenon has been described in amyotrophic lateral sclerosis (ALS), Alzheimer's disease, and Huntington's disease. Although overstimulation of NMDA receptors induces neurodegeneration, NMDA hypoactivity has been observed in psychotic states.<sup>5</sup>

### EVALUATION Neurologic symptoms

A few months after arriving at the residential facility, Ms. U develops dysarthria and drooling, which the treatment team initially interprets as secondary to high doses of clozapine. In the absence of clinical response after clozapine dose reduction and with the subsequent appearance of dysphagia with solid foods and liquids, Ms. U is evaluated by a ear, nose, and throat physician, and later by a neurologist. Both clinicians describe frontal release signs, anarthria, facial hypomimia, bilateral mild central paresis, absence of soft palate elevation with symmetrical phonation, decreased gag reflex and palatal atrophy, fasciculations, and bilateral lingual mandibular reflex and diagnose Ms. U with progressive bulbar palsy, a variant of ALS.

### Which symptoms are common in the early stages of ALS?

- difficulty swallowing
- speech problems
- cramping muscles
- all of the above

### The authors' observations

ALS is a progressive, degenerative neuromuscular condition of unknown etiology affecting the corticospinal tracts and the anterior horn of the spinal cord, leading to dysfunction of the upper and lower motor neurons.<sup>6</sup> It is more common in men, persons with diets rich in glutamate, and smokers.<sup>7,8</sup>

Riluzole is the only FDA-approved medication for ALS.<sup>9</sup> It interferes with the responses mediated by the NMDA receptor, stabilizes inactive sodium voltage-dependent channels, inhibits glutamate release from synaptic endings, and activates extracellular reuptake of glutamate, all of which are thought to confer a neuroprotective effect.<sup>10</sup>

### TREATMENT Psychosis improves

As suggested by the neurology team, we begin riluzole, 50 mg every 12 hours. At this time Ms. U also is taking clozapine, 600 mg/d; lithium, 1200 mg/d; and haloperidol, 6 mg/d; her psychiatric symptoms have not changed since the initial evaluation at the residential facility.

Seven months after initiating riluzole Ms. U is more receptive, less querulant, and no longer experiences delusions or hallucinations. At the same time, she develops an interest in her clinical status regarding her ALS diagnosis, which reflects improved insight. One year after starting riluzole, she is more cooperative and adherent with treatment. Ms. U is able to reestablish relationships with her family. Clozapine and haloperidol are tapered and discontinued. Ms. U's medication regimen includes risperidone, 1 mg/d; methotrimeprazine, 10 mg/d; venlafaxine, 75 mg/d; trazodone, 100 mg/d; and lithium, 600 mg/d, in addition to riluzole, 50 mg every 12 hours.

An assessment 18 months after starting riluzole describes a Positive and Negative Syndrome Scale (PANSS) score of 9 for positive symptoms, 11 for negative, 35 for the general psychopathology, and -2 for the composite (*Table 1*). Laboratory tests are normal except for a mild normocytic, normochromic anemia. MRI shows no detectable lesions or changes in comparison with previous images.

### What could account for Ms. U's improved psychotic symptoms?

- effect of ALS on the nervous system
- riluzole's effect on the glutamate system

Table 1

## Ms. U's clinical course

PANSS score	Treatment	Mental status
<b>Before starting riluzole</b>		
No PANSS reported	Clozapine, 600 mg/d; lithium, 1200 mg/d; haloperidol, 6 mg/d	Persistent auditory hallucinations. Persistent hallucinatory behavior. Paranoid delirious ideas. Negativism, mutism, and liability reactive to her psychosis state. Poor and flattened affect. Lack of disease awareness. Progressive social isolation. Loss of self care
<b>After starting riluzole</b>		
Positive subscale: 9 (below 5th percentile) Negative subscale: 11 (between 5th-25th percentile) General psychopathology subscale: 35 (between 5th-25th percentile) Composite score: -2 (between 25th-50th percentiles)	Riluzole, 50 mg every 12 hours; risperidone, 1 mg/d; methotrimeprazine, 10 mg/d; venlafaxine, 75 mg/d; trazodone, 100 mg/d; lithium, 600 mg/d	Re-establishes relationships with family because she no longer experiences paranoid delusions. Behavioral improvement. Allows physical proximity to nursing and medical personnel. Attention to physical appearance. Participates in social and recreational activities outside the hospital. Absence of auditory hallucinations. Affective improvement with appropriate responses. Realistic anxiety and fear about ALS diagnosis
ALS: amyotrophic lateral sclerosis; PANSS: Positive and Negative Syndrome Scale		

- c) passage of time
- d) reduction of antipsychotic dosage

**The authors' observations**

We present a patient with schizophrenia and a continuous pattern of relapses, functional and social impairment, and partial remission of her psychosis despite the use of multiple typical and atypical antipsychotics at therapeutic doses. Ms. U received treatment with clozapine at therapeutic doses for >6 months without sustained improvement. After beginning riluzole, a glutamate pathway antagonist, and with no other changes to her medication regimen, Ms. U experienced substantial improvement in her mental status. This was evidenced by a significant decline in her paranoid delusions, disappearance of auditory hallucinations, and substantial improvement on her social performance.

This fact is consistent with previous observations where modulation of the glutamate pathway has been associated with improvement in depression and anxiety

levels in different populations. This case report provides further evidence to the possibility that blocking this receptor is a promising approach to psychotic disorders.

**What other psychiatric disorders might respond to glutamate modulation?**

- a) bipolar disorder
- b) obsessive-compulsive disorder (OCD)
- c) Alzheimer's disease
- d) all of the above

**Riluzole for psychiatric illness**

Currently, there are 11 clinical trials investigating riluzole for psychiatric disorders, including OCD, depression, bipolar disorder, schizophrenia, and Tourette's syndrome.<sup>11</sup> Consistent with the altered glutamatergic neurotransmission implicated in mood and anxiety disorders, preliminary evidence suggests riluzole can effectively treat OCD, bipolar depression, unipolar depression, and comorbid OCD and depression (Table 2, page 58). Some

**Clinical Point**

After beginning riluzole and with no other changes in her medication regimen, Ms. U experienced improvement in her mental status

## Clinical Point

Drugs such as memantine, acamprosate, and lamotrigine act on the glutamatergic pathway

**Table 2**

### Evidence of efficacy of riluzole for OCD and depression

Study	Disorder	Findings
Pittenger et al, 2006 <sup>a</sup>	OCD	Brain imaging reveals elevated glutamate levels in OCD patients; agents that reduce glutamate hyperactivity may be effective
Coric et al, 2005 <sup>b</sup>	OCD	Among 13 patients with OCD who received riluzole, 54% demonstrated >35% reduction in Y-BOCS scores and 39% were considered treatment responders
Zarate et al, 2005 <sup>c</sup>	Bipolar depression	In an 8-week add-on study of riluzole in combination with lithium of 14 patients with bipolar depression, riluzole showed efficacy as measured by MADRS score and was well tolerated
Singh et al, 2004 <sup>d</sup>	Bipolar depression	Case report of a patient with bipolar II disorder and depression who had a good response to riluzole when lamotrigine was discontinued because of a maculopapular erythematous rash
Zarate et al, 2004 <sup>e</sup>	Unipolar depression	In a 6-week, open-label trial, 19 treatment-resistant depressed patients received riluzole; significant improvement measured by MADRS, CGI-S, and HAM-A were noted at weeks 3 through 6
Coric et al, 2003 <sup>f</sup>	Comorbid OCD and major depressive disorder	Case report of a patient with symptomatic OCD and depression who did not respond to appropriate pharmacotherapy, including augmentation strategies; adding riluzole significantly attenuated both obsessions and depressive symptoms

CGI-S: Clinical Global Impressions-Severity; HAM-A: Hamilton Anxiety Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; OCD: obsessive-compulsive disorder; Y-BOCS: Yale-Brown Obsessive Compulsive Scale

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investigators consider the glutamatergic pathway an essential target for future antidepressants and mood-stabilizing agents.<sup>12</sup>

Other drugs such as memantine, acamprosate, and lamotrigine act on this same pathway and therefore have a role in treating psychiatric and neurologic conditions. In the case of lamotrigine, the drug inhibits glutamate release through inhibition of voltage-dependent sodium and calcium channels<sup>13</sup> and postsynaptic AMPA receptors<sup>14</sup> and has been shown to effectively treat generalized epilepsies,<sup>15</sup> bipolar depression,<sup>13,16</sup> and depression and mood swings associated with Huntington's disease.<sup>17</sup>

Acamprosate's attenuation of hyperglutamatergic states through NMDA antagonism and metabotropic glutamate receptors and reduction of intracellular calcium release—therefore balancing the glutamatergic and GABAergic systems

and conferring neuroprotective properties—has been effective in patients with alcohol use disorders.<sup>18,19</sup>

Memantine and amantadine act through NMDA antagonism and by modulating dopaminergic transmission and may have clinical roles beyond dementia treatment.

### Schizophrenia-ALS comorbidity

Some investigators have suggested<sup>20</sup> the relative rarity of ALS in patients with schizophrenia is attributable to the neuroprotective effects of antipsychotics and antidepressants.<sup>21</sup> If this is true, it is possible resistance to antipsychotics among some schizophrenia patients may be underpinned by the degree of cell injury and therefore of neurodegeneration, which may be the case with Ms. U.

Controlled, randomized, double-blind studies are needed to confirm our team's

assumptions. Our observation is limited by the lack of standardized scale measurements to assess all schizophrenia domains before starting riluzole and Ms. U's clinical improvement could be associated with other factors such as passage of time or schizophrenia "burning out." However, clinical observation and description from family members and hospital staff are important to consider in this case.

The improvement in schizophrenia symptoms observed from a drug with no action on dopamine blockade—a quality observed in all antipsychotics<sup>22</sup>—reinforces the possibility that targeting different pathways involved in the genesis of schizophrenia is a reasonable topic for future research. The possible use of riluzole and other glutamate-modulating drugs might influence positive, negative, and cognitive symptoms of schizophrenia.

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## Clinical Point

Use of riluzole and other glutamate-modulating drugs might influence positive, negative, and cognitive symptoms

## Related Resources

- Kantrowitz JT, Javitt DC. Glutamate: new hope for schizophrenia treatment. *Current Psychiatry*. 2011;10(4):68-74.
- Vinson PN, Conn PJ. Metabotropic glutamate receptors as therapeutic targets for schizophrenia. *Neuropharmacology*. 2011. Epub ahead of print.

### Drug Brand Names

Acamprosate • Campral	Memantine • Namenda
Amantadine • Symmetrel	Olanzapine • Zyprexa
Clozapine • Clozaril	Riluzole • Rilutek
Haloperidol • Haldol	Risperidone • Risperdal
Ketamine • Ketalar	Sertindole • Serolect
Lamotrigine • Lamictal	Thioridazine • Mellaril
Lithium • Eskalith, Lithobid	Trazodone • Desyrel, Oleptro
Loxapine • Loxitane	Trifluoperazine • Stelazine
Methotrimeprazine • Nozinan	Venlafaxine • Effexor

### Disclosures

Dr. Millán-González is a consultant to AstraZeneca CAMCAR. Drs. Loizaga-Arníaz and Zúñiga-Montes report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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## Bottom Line

Riluzole, a glutamate pathway antagonist, may confer some benefit for patients with treatment-resistant schizophrenia. It is unknown whether the effect of riluzole is due to a neuroprotective effect and whether changes in glutamate pathways could lead to secondary changes in other neurotransmitter pathways.

## ONLINE ONLY

Table 2

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