Published in final edited form as:

Psychosomatics. 2013 ; 54(5): 488–492. doi:10.1016/j.psych.2013.02.002.

Delayed amnesic syndrome after riluzole use in major depressive disorder: a case report

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Conflict of Interest Disclosure

Dr. Sanacora has received consulting fees from AstraZeneca, Avanier Pharmaceuticals, Bristol-Myers Squibb, Evotec, Eli Lilly & Co., Hoffman La-Roche, Novartis, and Novum Pharmaceuticals over the last 24 months. He has also received additional grant support from AstraZeneca, Bristol-Myers Squibb, and Hoffman La-Roche, Merck & Co., over the last 24 months. In addition he is a co-inventor on filed patent application by Yale University (PCTWO06108055A1).

Dr Fava has received research support from Abbott Laboratories, Alkermes, Aspect Medical Systems, Astra-Zeneca, BioResearch, BrainCells, Inc., Bristol-Myers Squibb Company, Cephalon, Clinical Trial Solutions, LLC, Eli Lilly & Company, EnVivo Pharmaceuticals, Inc., Forest Pharmaceuticals Inc., Ganeden, GlaxoSmithKline, J & J Pharmaceuticals, Lichtwer Pharma GmbH, Lorex Pharmaceuticals, NARSAD, NCCAM, NIDA, NIMH, Novartis, Organon Inc., PamLab, LLC, Pfizer Inc, Pharmavite, Roche, Sanofi-Aventis, Shire, Solvay Pharmaceuticals, Inc., Synthelabo, and Wyeth-Ayerst Laboratories. He has served as an advisor and consultant to Abbott Laboratories, Affectis Pharmaceuticals AG, Amarin, Aspect Medical Systems, Astra-Zeneca, Auspex Pharmaceuticals, Bayer AG, Best Practice Project Management, Inc, BioMarin Pharmaceuticals, Inc., Biovail Pharmaceuticals, Inc., BrainCells, Inc, Bristol-Myers Squibb Company, Cephalon, Clinical Trials Solutions, LLC, CNS Response, Compellis, Cypress Pharmaceuticals, Dov Pharmaceuticals, Eisai, Inc., Eli Lilly & Company, EPIX Pharmaceuticals, Euthymics Bioscience, Inc., Fabre-Kramer, Pharmaceuticals, Inc., Forest Pharmaceuticals Inc., GlaxoSmithKline, Grunenthal GmbH, Janssen Pharmaceutica, Jazz Pharmaceuticals, J & J Pharmaceuticals, Knoll Pharmaceutical Company, Labopharm, Lorex Pharmaceuticals, Lundbeck, MedAvante Inc., Merck, Methylation Sciences, Neuronetics, Novartis, Nutrition 21, Organon Inc., PamLab, LLC, Pfizer Inc, PharmaStar, Pharmavite, Precision Human Biolaboratory, Prexa Pharmaceuticals, Inc., PsychoGenics, Psylin Neurosciences, Inc., Ridge Diagnostics, Inc., Roche, Sanofi-Aventis, Sepracor, Schering-Plough, Solvay Pharmaceuticals, Inc., Somaxon, Somerset Pharmaceuticals, Synthelabo, Takeda, Tetragenex, TransForm Pharmaceuticals, Inc., Transcept Pharmaceuticals, Vanda Pharmaceuticals Inc, Wyeth-Ayerst Laboratories. He has received speaking and publishing honoraria from Adamed, Co., Advanced Meeting Partners, American Psychiatric Association, American Society of Clinical Psychopharmacology, Astra-Zeneca, Belvoir, Boehringer-Ingelheim, Bristol-Myers Squibb Company, Cephalon, Eli Lilly & Company, Forest Pharmaceuticals Inc., GlaxoSmithKline, Imedex, Novartis, Organon Inc., Pfizer Inc, PharmaStar, MGH Psychiatry Academy/Primedia, MGH Psychiatry Academy/Reed-Elsevier, UBC, and Wyeth-Ayerst Laboratories. He holds equity in Compellis. He currently holds a patent for SPCD and a patent application for a combination of azapirones and bupropion in MDD, and has received copyright royalties for the MGH CPFQ, SFI, ATRQ, DESS, and SAFER diagnostic instruments.

Dr Mischoulon has received research support from Nordic Naturals, Ganeden, the Bowman Family Foundation, and Fisher Wallace. He has served as a consultant to Bristol-Meyers-Squibb Company and Methylation Sciences, Inc. He has received writing honoraria from PamLab and Nordic Naturals and speaking honoraria from Nordic Naturals. He has received royalties from Back Bay Scientific for PMS Escape, and royalties from Lippincott Williams & Wilkins, for textbook "Natural Medications for Psychiatric Disorders: Considering the Alternatives" (David Mischoulon and Jerrold F Rosenbaum, Eds.). He has received honoraria from the MGH Psychiatry Academy.

All other authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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Introduction

Treatment-resistant depression (TRD) remains a common problem, with 29–46% of depressed patients failing to respond sufficiently to adequate trials of antidepressant medications.¹ Recently, several open-label clinical trials of riluzole, an antiglutamatergic drug approved by the US Food and Drug Administration (FDA) for treatment of amyotrophic lateral sclerosis (ALS), have revealed antidepressant effects in individuals with major depressive disorder, generalized anxiety disorder, and obsessive-compulsive disorder.^{2–5}

The most common side effects of riluzole (at doses of 100mg/day) include asthenia (19.2%), nausea (16.3%), and decreased lung function (10.2%); other common but less frequent (<10%) side effects include dizziness, diarrhea, abdominal pain, vomiting, vertigo, oral paresthesia, anorexia, insomnia, somnolence, and psychiatric symptoms such as depression⁶. A more serious and rare adverse effect, amnesic syndrome, has been previously reported twice, in the context of overdose. In the first case, a woman with Huntington's disease developed delayed amnesia that persisted for over a year, four days after ingesting 3g of riluzole.⁷ In the second case, a woman with Huntington's disease developed severe amnesic syndrome with anterograde and retrograde amnesia as well as attention and short-term memory deficits, four days after ingesting 2.8g of riluzole.⁸ In the latter case, the patient's cognitive functions improved gradually and returned to baseline within a year of the intoxication⁸. We report here a case of global amnesia related to as-directed use of riluzole in the setting of a randomized clinical trial (RCT).

Case Discussion

A multicenter randomized, double-blind controlled trial of riluzole as adjunctive therapy for treatment-resistant major depressive disorder (MDD) is currently in progress through our institutions (NCT01204918). In brief, participants who experience an inadequate response to an SSRI or SNRI are randomized to receive 50mg of adjunctive riluzole or placebo twice daily for eight weeks, followed by 50mg of open-label riluzole twice daily for three months.

Our patient is a 53-year-old woman with MDD who completed the double-blind portion of the study and entered the follow-up phase. Her medical history was noted for fibromyalgia, and distant substance abuse (including alcohol, marijuana, cocaine, and heroin) in stable remission. Prior to enrollment, the patient's physical examination and labs (including hepatic enzymes, drugs of abuse, complete blood count, urinalysis, thyroid-stimulating hormone, pregnancy test, and basic metabolic panel) were within normal limits. At the study baseline visit, the patient had a score of 28 on the Montgomery-Asberg Depression Rating Scale (MADRS). Her MADRS score dropped to 9 by the conclusion of the double-blind treatment phase, and she then entered the open-label continuation phase. After eight weeks on open-label 100mg riluzole and 150mg sertraline with continued good response (her MADRS score remained in the single digits, but had worsened to 12 at her discontinuation visit), the patient was discontinued from riluzole without tapering due to moderate and intermittent nausea and vomiting occurring within 10 minutes of ingesting the medication. These side effects had emerged about two weeks prior to stopping medication.

Per the protocol, if subjects reported significant side effects of any sort in the double-blind phase, the riluzole/placebo dose could be decreased to 50 mg/day (one riluzole or placebo pill daily), with rechallenging at 100 mg/day the following week. Subjects who could not tolerate a minimum riluzole dose of 50 mg/day would be discontinued from the study. In the open label treatment phase, side effects were managed at the clinician's discretion. In this case, the clinician judged it best to discontinue riluzole.

Three days after discontinuing riluzole, the patient set out for a short walk, but ended up traveling seven miles and losing her way. She was found by the police in a fugue state, and could not remember her name, address, or location. She was taken to a community hospital immediately, and admitted with a diagnosis of global amnesia, presumed secondary to a seizure. The patient was conscious and alert upon arrival, but had no identification. However, she had an address book, in which the police found her family's contact information. The treatment team then obtained the medical history from the patient's family and primary care physician.

On the medical floor, she was started on phenytoin for presumed seizure and gabapentin for fibromyalgia-related pain. She refused magnetic resonance imaging (MRI) and lumbar puncture, but agreed to a head computed tomography (CT) scan, electrocardiogram (EKG), electroencephalography (EEG), and x-rays, all of which were normal. Upon admission to the hospital, blood tests were noted for a mild elevation of liver enzymes alanine transaminase (ALT) (72 U/L) and aspartate transaminase (AST) (69 U/L), and elevation of troponin I (TRP-I) (0.15 ng/mL, and 0.14 ng/mL upon repeat 8 hours later) and creatine phosphokinase (CPK) (632 U/L), the latter of which returned to normal (220 U/L) after two days. Serum creatinine at admission was 1.53mg/dL, glomerular filtration rate (GFR) was 32 mL/min, and serum calcium was 10.4 mg/dL. These all normalized within 2 days. No other electrolyte abnormalities were recorded. No further repeat tests of TRP-I were obtained.

Toxicity screens were negative for serum alcohol, salicylates, and acetaminophen, and for urine amphetamines, barbiturates, cannabinoids, benzodiazepines, cocaine, opiates, phencyclidine, MDMA (3,4-methylenedioxy-methamphetamine), and methadone.

The patient was unable to recognize a close relative who came to visit during the first few days of hospitalization, but no signs of delirium were ever recorded. Her vital signs were normal throughout her participation in our study and hospitalization. No unusual movements such as automatisms or tremor were noted. The patient complained occasionally of fibromyalgia-related pain, but had no other sensory or motor complaints.

The patient's memory began to recover after four days. By the sixth day of hospitalization, the patient had fully recovered and was discharged in good condition, on sertraline 150mg daily. Of interest, no mention of riluzole was ever made in the hospital records. Mild rhabdomyolysis was listed in the discharge diagnosis, based on the elevated CPK and troponin I, and because the patient's overall workup did not suggest a cardiac event.

The patient contacted our site four days following her discharge from the hospital, and spoke with a study physician, who obtained the details of her emergency hospitalization. During this telephone interview, the patient's mental status exam was stable, with no cognitive abnormalities, or suicidal or homicidal ideation. She reported a good mood, denied any past episodes of this type, and was advised to remain on sertraline and not to take riluzole again. Three months later, she remains in follow-up at our institution, currently on 200mg/day sertraline monotherapy. She had a mild depressive worsening at the time she resumed her visits with us, but at her most recent visit, now more than 3 months removed from the amnesic episode, she endorsed a better mood, mild insomnia, some fidgetiness, and passive suicidal ideation. The patient can recall leaving her house to go for a walk on the day of admission, but has no recollection of the events between then and the time she recovered her memory in the hospital.

Discussion

This is a case of delayed (after three days) amnesia following discontinuation of riluzole, with symptoms persisting for six days. The two previously reported cases of riluzole-

associated amnesia occurred in the context of overdose in patients with Huntington's disease^{7,8}. Both cases involved delayed onset amnesia, emerging about 4 days following overdose, and both with sequelae lasting for at least one year^{7,8}. To our knowledge, this is the first reported case of amnesia in the context of discontinuation of riluzole following as-directed use (pill counts were performed at every visit, and the patient demonstrated 100% compliance).

Given the known half-life of riluzole (9–15 hours) and the delay of emergence of amnesia, most of the riluzole should have been out of our patient's system by the time the symptoms emerged, which raises the possibility that she may have been a slow metabolizer of the drug. Riluzole is metabolized in the liver primarily via hydroxylation by cytochrome P450 1A2, to form an N-hydroxyriluzole metabolite that undergoes glucuronidation at the hydroxylamine group⁹. Riluzole may have been building up in the patient's system over eight weeks to a toxic level, as suggested by the emergence of intermittent vomiting for two weeks prior to the event, and elevated liver enzymes, which had been normal per our routine labs prior to initiating riluzole. CYP genotyping data were not available for the patient, so we do not know whether a polymorphism may have been a factor in this adverse effect. However, genetic polymorphisms do not seem to affect riluzole metabolism, at least in ALS patients.¹⁰

The rhabdomyolysis and elevated liver enzymes, both known side effects of riluzole, may have been due to the patient taking riluzole in excess, though her documented adherence argues against this. The reasons for elevated CPK are unclear, but may be explained by possible increased activity during the fugue state.

Because the study is ongoing, we cannot break the blind to determine whether the patient was taking riluzole or placebo during the double blind phase. If the patient was randomized to riluzole, we might have expected onset of side effects during the double-blind phase, whereas randomization to placebo would better explain the onset of the GI complaints in the open label phase. The patient's good response in the double-blind phase suggests randomization to riluzole, but we cannot rule out a placebo response, which is common in depression trials. It is also possible that the patient was not a particularly slow metabolizer, and accumulation of toxic metabolite occurred gradually during both phases of the study.

The Haaxma et al⁷ report suggested that since riluzole's half life is short, memory loss could have resulted from a long-lasting functional change of hippocampal interneuron signaling. Although the exact mechanism of riluzole's neuroprotective and possible antidepressant action remains unclear, it is thought to involve two effects modulating glutamate neurotransmission. The original mechanism proposed for the effect was inhibition of glutamate release via blockage of presynaptic sodium channels¹¹; this may limit the amount of glutamate released into the extracellular space and thus limit levels of excitotoxicity. More recent data, however, suggests riluzole's primary therapeutic action is, at least in part, related to drug-induced enhancement of glial cells' ability to clear extracellular glutamate. Glial cells clear the vast majority of glutamate from the extracellular space through excitatory amino-acid transporters (EAATs). Riluzole has been shown to increase the expression and function of glial cell glutamate transporter GLT-1, the rodent version of human excitatory amino-acid transporter (EAAT2)^{12–14}. Through either or both of these mechanisms, riluzole may alter levels of extracellular glutamate, as well as the relative activation of N-Methyl-D-aspartic acid (NMDA) to AMPA (2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid) receptors or the relative activation of synaptic to extrasynaptic NMDA receptors.

Changes in relative levels of extracellular glutamate, especially if increased levels are seen in the extrasynaptic space, are likely to have significant effects on memory. Glutamate receptor stimulation has been shown to be a central process in the formation of long-term potentiation (LTP) and long-term depression (LTD), two processes important to hippocampal memory formation. Recent studies have specifically highlighted the importance of relative synaptic and extrasynaptic stimulation in the formation of LTP and LTD¹⁵. Ceftriaxone-induced GLT-1 up-regulation significantly reduced the magnitude of LTP at mossy fiber-to-CA3 pyramidal cell (MF-CA3) synapses but not at Schaffer collateral-CA1 synapses¹⁶.

Thus, the delayed onset of amnesia in the prior case reports^{7,8} as well as in our patient may be due to altered LTP and LTD-like processes resulting from changes in the relative levels of extracellular glutamate related to either the ongoing buildup of clearance capabilities, or rapid changes in glutamate neurotransmission following medication washout. Both patients from the prior case reports^{7,8} had effects lasting up to one year, suggesting relatively severe structural damage, probably related to the high doses consumed. Their recoveries may also have been slower due to their underlying Huntington's disease.

We must also consider the possibility that sudden withdrawal from riluzole led to the global amnesia. Malgouris et al¹⁷ showed that riluzole reverses memory loss in gerbils following ischemic events. If glutamic acid contributes to neuronal degeneration of the hippocampus following ischemia, riluzole may protect the brain from toxic effects of ischemia, and prevent neuronal loss. It is possible that with withdrawal, changes in the expression of EAAT2 would cause changes in the ratio of extrasynaptic to synaptic glutamate levels that would have effects on memory formation. In our patient, if riluzole was benefiting her memory, the sudden withdrawal may have precipitated amnesia. This would require further investigation.

Wide variations in individual riluzole peak serum concentrations have been detected¹⁸. This could be related to differences in CYP 1A2 activity, but also could be due to smoking, diet, and variability in oral bioavailability. The patient, however, is a non-smoker and reported no unusual dietary practices or changes during her participation in the study. Her weight during her treatment period with our group has fluctuated between 143 and 150 lbs, which does not suggest any nutritional problems. Likewise, she denied taking any illicit substances or other CYP 1A2 active medications that might have gone undetected in the toxicity screen.

The differential diagnosis must also include a cardiovascular accident (CVA), which cannot be fully ruled out by the head CT alone, or a partial seizure, as was suspected upon admission. Riluzole has demonstrated anticonvulsant effects in animal models^{19,20}. However, the patient had no history of cardiovascular or seizure disorder, and there are no reports of riluzole withdrawal-associated seizures, all of which argues against epileptiform activity, particularly given the normal EEG. Other psychiatric causes such as a fugue state (dissociative fugue) could also be possible. The patient denied any stressors around the time of admission, so it seems unlikely that situational factors contributed to her presentation.

Suggestions for Clinical Care and Further Study

Physicians who prescribe riluzole should inform patients about the possibility of amnesia in the context of overdose or sudden discontinuation. In particular, sudden onset of severe nausea or vomiting could be a harbinger of toxicity and in these cases special precautions should be taken. Patients who wish to discontinue riluzole should do so under physician supervision, with careful observation for any cognitive impairment. Further research into the mechanism of riluzole-associated amnesia is warranted.

Acknowledgments

This study was supported by the NIMH through R01 MH08055 (GS) and the Connecticut Department of Mental Health and Addiction Services (GS).

Study drug was supplied by Sanofi-Aventis.

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