

# Riluzole Augmentation in Treatment-Resistant Obsessive–Compulsive Disorder: An Open-Label Trial

Vladimir Coric, Sarper Taskiran, Christopher Pittenger, Suzanne Wasylink, Daniel H. Mathalon, Gerald Valentine, John Saksa, Yu-te Wu, Ralitza Gueorgieva, Gerard Sanacora, Robert T. Malison, and John H. Krystal

**Background:** Most patients with obsessive–compulsive disorder (OCD) show only partial reduction of symptoms with standard therapy. Recent imaging data suggests glutamatergic dysfunction in the corticostriatal pathway in OCD. We investigated the efficacy of augmentation therapy with riluzole, a glutamate-modulating agent, in treatment-resistant OCD.

**Methods:** Thirteen patients aged between 18 and 65 years with a primary diagnosis of OCD that had proven resistant to standard treatment were treated with the addition of riluzole to their existing pharmacotherapy. Yale–Brown Obsessive Compulsive Scale (Y-BOCS), Hamilton Depression Inventory (HAM-D), and Hamilton Anxiety Inventory (HAM-A) scores were obtained weekly.

**Results:** Thirteen treatment-resistant OCD patients received riluzole 50 mg twice a day. Y-BOCS scores improved significantly over time. Of 13 patients, 7 (54%) demonstrated a >35% reduction in Y-BOCS scores, and 5 (39%) were categorized as treatment responders. HAM-D and HAM-A scores for the group also significantly improved over time. Riluzole was well tolerated with no serious adverse effects noted.

**Conclusions:** Riluzole appears to have significant antiobsessional, antidepressant, and antianxiety properties. The addition of this agent may be of practical clinical benefit in patients with OCD.

**Key Words:** Anxiety disorders, glutamate, obsessive–compulsive disorder, major depressive disorder, riluzole

Although serotonin reuptake inhibitors (SRIs), cognitive-behavioral therapy (CBT), and augmentation with dopamine antagonists have proven efficacy in the treatment of obsessive–compulsive disorder (OCD), treatment-resistant OCD remains a common and debilitating problem. Current clinical interventions significantly reduce symptoms in approximately 40%–60% of patients with OCD; however, a substantial number of patients remain dramatically symptomatic even with the combination of pharmacotherapy and CBT (Jenike 2004). Moreover, a therapeutic response in most treatment trials is defined as symptom reduction by 20%–40% with many treatment responders remaining markedly symptomatic (Jenike 2004). Treatment-resistant OCD is one of the few psychiatric indications for neurosurgical intervention. Novel therapeutic strategies are urgently needed.

This pilot study is based on preclinical and neuroimaging studies that implicate glutamatergic hyperactivity in the increased regional brain metabolism associated with OCD (Baxter et al 2001; McGrath et al 2000). Neuroimaging studies have consistently identified increased blood flow, glucose metabolism, and brain activity in the cortico–striato–thalamic (CST) network of individuals with OCD (Baxter et al 2001). Given the stoichiometric relationship between cerebral glucose metabolism and glutamatergic neurotransmission (Magistretti et al 1999), a drug that reduces glutamatergic neurotransmission may attenuate the regional CST hyperactivity observed in patients with OCD. Consistent with a glutamatergic hypothesis, recent <sup>1</sup>H magnetic resonance spectroscopy (<sup>1</sup>H-MRS) studies suggest that glutamate

levels are elevated in components of the CST in OCD patients, and glutamatergic elevations decline with effective treatment (Rosenberg et al 2000). Normalization of CST activity may be a final common pathway for treatment.

We hypothesized that a drug that reduced glutamatergic neurotransmission would augment the efficacy of SRIs in treating OCD symptoms. Riluzole is a potent antiglutamatergic agent that reduces glutamatergic neurotransmission in several ways, including inhibition of glutamate release, inactivation of voltage-dependent sodium channels in cortical neurons, and blockade of GABA reuptake (Jehle et al 2000; Urbani and Belluzzi 2000). We initiated an open-label study of riluzole augmentation therapy in patients with treatment-resistant OCD to test the preliminary efficacy and safety of an antiglutamatergic strategy in this population. We have previously published a case report describing a significant improvement in mood and anxiety symptoms using this approach (Coric et al 2003).

## Methods and Materials

Thirteen patients were recruited from the Yale OCD Research Clinic. Patient characteristics and inpatient–outpatient status are listed in Table 1. All patients provided written informed consent before study participation. The study was approved by the Yale University Human Investigations Committee, New Haven, Connecticut. Patients aged between 18 and 65 with a primary DSM-IV diagnosis of OCD who had failed to clinically respond to at least 8 weeks of treatment with SRIs were eligible for study participation. Treatment failure was defined by a Yale–Brown Obsessive Compulsive Scale (Y-BOCS) score >16 despite at least 8 weeks of treatment with the maximum tolerated dose of an SRI medication. Additionally, OCD symptoms had to be present for at least 1 year and at least of moderate severity on the Clinical Global Impression Scale severity of illness item. Patients with a primary psychotic disorder, prior psychosurgery for OCD, illicit substance use over the past 1 month, seizure disorder, significant head trauma, acute medical illnesses, or elevated baseline liver function tests (LFTs; i.e., greater than twice the upper limits of normal) were excluded from study participation. Diagnoses were confirmed using the Structured Clinical Interview for Axis I

From the Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut.

Address reprint requests to Vladimir Coric, M.D., Clinical Neuroscience Research Unit, Yale University School of Medicine/Connecticut Mental Health Center, 34 Park Street, New Haven CT 06519; E-mail: vladimir.coric@yale.edu.

Received August 19, 2004; revised January 27, 2005; accepted April 22, 2005.

**Table 1.** Clinical Characteristics of Patients with OCD Treated with Riluzole Addition to SRI

Patient No./Age(y)/Sex/ Ethnicity	Age at Onset (y)	Duration (y)	Type of Symptoms	Comorbid Diagnoses	Psychiatric Family History
001/34/M/W <sup>a</sup>	11	23	Agg, sex	MDD	OCD (p grandfather); anorexia (sister)
002/53/F/W <sup>a</sup>	48	5	Agg, sex	MDD, Tic	Suicide (p grandfather, p uncle)
003/29/M/W	10	19	Agg, ctm, rel, cln/was, chk, cnt, ntk	MDD, Tic	OCD (father)
004/50/F/W	23	27	Sym/ext, ord/arr	MDD	None
005/36/M/W <sup>a</sup>	22	14	Chk, rpt, ntk	None	OCD (father), MDD (mother), panic (father); GAD (brother, sister)
006/23/F/W <sup>a</sup>	22	1	Som, ctm, cln/was	MDD	None
007/61/F/W	30	31	Hrd, sym/ext, chk, rpt, cnt, ord/arr, ntk	None	OCD (mother); alcohol abuse (father)
008/30/M/W <sup>a</sup>	16	14	Agg, sex, rel, chk, cnt	MDD	None
009/61/F/AA	43	18	Hrd, rel	MDD	None
010/29/F/W <sup>a</sup>	18	11	Cln/was, cnt, sym/ext, chk, cnt, rpt, hrd	MDD	OCD (m grandfather); schizophrenia (p grandmother)
011/46/F/W <sup>a</sup>	24	22	Ctm, hrd, cln/was, chk, sym/ext	None	None
012/30/F/W	22	8	Chk, sym/ext, rpt, ord/arr, ntr	MDD	None
013/50/M/W <sup>a</sup>	21	29	Sym/ext, ctm, cln/was, hrd, chk, rpt, ord/arr, ntk	MDD	MDD (father, m grandmother + father, p aunt + uncle); alcohol abuse (father)

AA, African-American; Agg, aggressive; chk, checking; cln/wsh, cleaning/washing; cnt, counting; ctm, contamination; F, female; GAD, generalized anxiety disorder; hrd, hoarding; M, male; m, maternal; MDD, major depressive disorder; ntr, need to touch, tap, OCD, obsessive-compulsive disorder; ord/arr, ordering/arranging; or rub; p, paternal; panic, panic disorder; rel, religious; rpt, repeating; sex, sexual; som, somatic; sym/ext, symmetry/exactness; Tic, tic disorder, W, Caucasian; and y, years.

<sup>a</sup>Treated as inpatient.

DSM-IV Disorders (1997). Major depression was the most common comorbid diagnosis, occurring in 10 of the 13 patients. Patients had to have failed at least 8 weeks of treatment on their current SRI medication. Concomitant psychotropic medications were permitted only if prescribed at a stable dose for at least 1 month before beginning the trial.

Study duration was initially 6 weeks. After results from initial subjects suggested ongoing therapeutic response with time, the study was extended to 9 weeks and then to 12 weeks.

Riluzole was initiated and maintained at a dose of 50 mg twice a day. Subjects were evaluated weekly with clinician-administered rating scales: Y-BOCS, Clinical Global Impression/Global Improvement item (CGI/GI), Hamilton Depression Inventory (HAM-D), and Hamilton Anxiety Inventory (HAM-A). Liver function tests were monitored at baseline and every 3 weeks throughout the study. Because of the variable time of treatment (6–12 weeks), Y-BOCS, HAM-D, and HAM-A were analyzed in SAS PROC MIXED using mixed-effects models with time (baseline to week 9) as fixed effect and a structured variance-covariance pattern matrix (Brown and Prescott 1999; Gueorguieva and Krystal 2004). The CGI/GI was analyzed using the same model with time (baseline to week 7) as fixed effect. The best fitting variance-covariance matrix according to the Akaike Information Criterion was selected.

## Results

Thirteen patients entered the study, and only one subject, a treatment responder, dropped out at week 9 because of a family situation. Previous SRI treatment trials, history of augmentation strategies, previous CBT, dosage of concomitant medications, and outcome variables for each patient are shown in Table 2. The mean number of previously failed medication trials included 3.5 ( $\pm 1.7$ ) SRI/serotonin-norepinephrine reuptake inhibitor (SNRI)/tricyclic trials and 1.3 ( $\pm 1.5$ ) dopamine antagonist augmentation trials. Additionally, 12 of 13 subjects failed previous trials of CBT. Mean doses of concomitant medications during the study, dosed

alone or in combination, included the following: fluoxetine 80 mg ( $n = 4$ ), clomipramine 262.5 mg ( $n = 4$ ), escitalopram 20 mg ( $n = 2$ ), fluvoxamine 300 mg ( $n = 3$ ), buspirone 30 mg ( $n = 1$ ), risperidone 5 mg ( $n = 1$ ), olanzapine 11.3 mg ( $n = 2$ ), quetiapine 50 mg ( $n = 1$ ), and clonazepam 1.3 mg ( $n = 5$ ). Mean Y-BOCS score of patients entering the study was 30.7 ( $\pm 6.6$ ), indicating severe OCD symptoms. Data from one patient was previously published as a case report (Coric et al 2003).

Figure 1 illustrates the mean Y-BOCS score for all study participants. Mean Y-BOCS for the group at baseline was 30.7 ( $\pm 6.6$ ) and at end of study was 17.7 ( $\pm 8.6$ ), representing an overall 42% reduction for the entire cohort. Y-BOCS scores improved significantly over time ( $F_{1,11.1} = 19.78, p = .001$ ). Of the 13 patients, 7 (54%) demonstrated a >35% reduction in Y-BOCS scores; 5 of 13 (39%) were categorized as treatment responders, as defined by a 35% or greater reduction in baseline Y-BOCS, a final Y-BOCS of 16 or less, and consensus of the treating clinicians. Percent reduction in baseline Y-BOCS scores at the end of the study ranged from 38% to 76% in responders. Two of the five responders were characterized predominantly by hoarding behaviors. Clinician administered CGI/GI scores significantly improved over time ( $F_{1,16.2} = 20.99, p = .0003$ ). Mean baseline CGI/GI was 4 ( $\pm 0$ ), week 6 CGI/GI was 3.2 ( $\pm .6$ ), week 9 CGI/GI was 2.66 ( $\pm .5$ ), and week 12 CGI/GI was 2.33 ( $\pm 1$ ).

Mean HAM-D at baseline was 30 ( $\pm 13.7$ ) and at end of study was 19.7 ( $\pm 6.0$ ). HAM-D scores for the entire group improved significantly over time ( $F_{1,10.8} = 9.12, p = .012$ ); 6 of 13 patients demonstrated clinically significant improvements in HAM-D scores with 36%–83% reductions in baseline HAM-D scores by the end of the study. Mean HAM-A at baseline was 18.2 ( $\pm 6.2$ ) and at end of study was 12 ( $\pm 2.5$ ). HAM-A scores improved significantly over time ( $F_{1,11.2} = 7.9, p = .017$ ). Riluzole was well tolerated, and no serious adverse events were noted. Asymptomatic, transient increases in at least one LFT were noted in 4 of 13 patients. One patient experienced a ninefold increase in alanine aminotransferase (ALT); repeat ALT in that patient revealed a

**Table 2.** Treatment Data of Patients with OCD treated with Riluzole Addition to SRI

Pt No.	No. of Previous Medication Trials	Previous SRI Treatment Trials	Previous Neuroleptic Augment	Previous Behavioral Therapy	Current SRI	Daily SRI Dose	Concomittant Medications	CGI Treatment Response	Pre/Post YBOCS Score	Pre/Post HAM-D Score	Pre/Post HAM-A Score
1 <sup>b</sup>	4	Citalopram, fluvoxamine, venlafaxine	Yes	Yes	Fluvoxamine	300 mg	Clonazepam 1 mg qhs	3	19/11 <sup>e</sup>	52/33 <sup>e</sup>	22/20
2 <sup>b</sup>	3	Sertraline	Yes	No	Clomipramine	350 mg	Olanzapine 7.5 mg qhs	4	18/14 <sup>e</sup>	37/25	18/15
3 <sup>b</sup>	6	Fluvoxamine, fluoxetine, paroxetine, citalopram, sertraline, venlafaxine	Yes	Yes	Clomipramine	225 mg	Bupirone 30 mg qhs	3	35/34	12/12	7/3 <sup>e</sup>
4 <sup>a</sup>	7	Sertraline, fluoxetine, citalopram, paroxetine, escitalopram, clomipramine, fluvoxamine	Yes	Yes	Escitalopram	20 mg	None	4	40/39	25/29	14/31
5 <sup>b</sup>	4	Fluvoxamine, clomipramine, buspirone	No	Yes	Fluoxetine	80 mg	Quetiapine 50 mg qhs	3	32/28 <sup>e</sup>	15/13	14/14
6 <sup>a</sup>	2	Escitalopram	Yes	Yes	Escitalopram	20 mg	Risperidone 5 mg qhs	2	37/16 <sup>e</sup>	56/16 <sup>e</sup>	25/8 <sup>e</sup>
7 <sup>c</sup>	2	Fluoxetine	No	Yes	Fluoxetine	80 mg	None	3	31/13 <sup>e</sup>	17/20	13/12
8 <sup>c</sup>	5	Sertraline, fluvoxamine, paroxetine, clomipramine	Yes	Yes	Clomipramine	250 mg	Olanzapine 15 mg qhs, clonazepam .5 mg tid	3	35/32	28/30	22/15
9 <sup>c</sup>	3	Fluvoxamine, fluoxetine	No	Yes	Fluoxetine	80 mg	None	1	33/8 <sup>e</sup>	41/11 <sup>e</sup>	29/10 <sup>e</sup>
10 <sup>c</sup>	2	Fluvoxamine	Yes	Yes	Fluvoxamine	300 mg	Clonazepam .5 mg bid	3	32/20 <sup>e</sup>	31/20 <sup>e</sup>	19/15
11 <sup>d</sup>	1	Fluoxetine	No	Yes	Fluoxetine	80 mg	Clonazepam .5 mg qid	2	34/20 <sup>e</sup>	18/3 <sup>e</sup>	11/4 <sup>e</sup>
12 <sup>c</sup>	4	Fluoxetine, escitalopram, fluvoxamine, paroxetine	Yes	Yes	Clomipramine	225 mg	Topiramine 50 mg bid, Clonazepam 1 mg qhs	2	28/21	25/19	18/11 <sup>e</sup>
13 <sup>c</sup>	3	Paroxetine, fluvoxamine, clomipramine	No	Yes	Fluvoxamine	300 mg	None	2	25/12 <sup>e</sup>	33/18 <sup>e</sup>	24/9 <sup>e</sup>

Bid, two times a day; CGI, Clinical Global Impressions; Ham-A, Hamilton Anxiety Rating Scale; Ham-D, Hamilton Depression Rating Scale; OCD, obsessive-compulsive disorder; qid, four times a day; qhs, given at bedtime; SRI, serotonin reuptake inhibitor; tid, three times a day; YBOCS, Yale-Brown Obsessive Compulsive Scale.

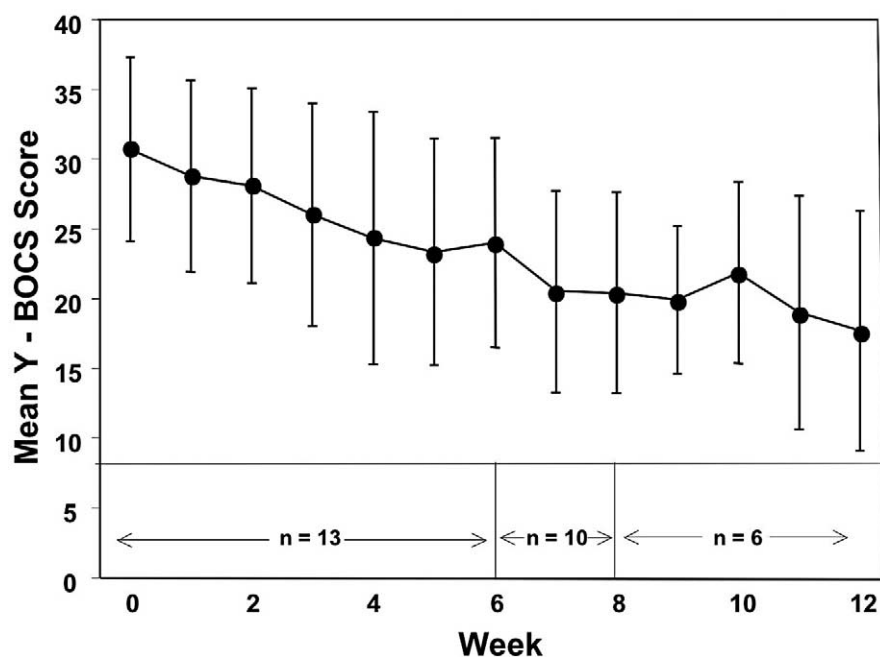
<sup>a</sup>Study duration 6 weeks.

<sup>b</sup>Study duration 9 weeks.

<sup>c</sup>Study duration 12 weeks.

<sup>d</sup>Subject enrolled for 12 week study, responded to treatment, and dropped from study at week 9 due to family situation (represents the only study drop-out).

<sup>e</sup>>35% reduction in pre/post rating scales.



**Figure 1.** Mean Yale–Brown Obsessive Compulsive Scale (Y-BOCS) score in patients with serotonin reuptake inhibitor-resistant obsessive-compulsive disorder treated with riluzole addition. \*Y-BOCS scores improved significantly over time ( $F_{1,11.1} = 19.78, p = .001$ ).

fourfold increase that normalized to within two times the upper limits of normal by week 3. Mean baseline aspartate aminotransferase AST, ALT, and alkaline phosphatase (Alk Phos) were 19.1 ( $\pm 5.7$ ), 22.9 ( $\pm 12.3$ ), and 75 ( $\pm 13.5$ ), respectively; mean week 6 AST, ALT, and Alk Phos were 22 ( $\pm 13.84$ ), 35.3 ( $\pm 28.3$ ), and 83.7 ( $\pm 24.4$ ).

## Discussion

This open-label study suggests that directly attenuating glutamatergic activity may be efficacious in treatment-resistant OCD. Furthermore, the observed improvements in Y-BOCS, HAM-D, and HAM-A scores after addition of riluzole is consistent with recent clinical reports suggesting that modulation of glutamatergic pathways using the antiglutamatergic agent riluzole may provide symptom relief in anxiety and mood disorders (Coric et al 2003; Sanacora et al 2004b; Zarate et al 2004).

Effective OCD treatment with SRI medications has been observed to lead to a reduction in glutamatergic tone in the CST network (Rosenberg et al 2000). Although OCD has been associated with increased activity in the CST network, it may not be associated with a global increase in glutamatergic function. In fact, a recent report shows reduced glutamate concentrations in the anterior cingulate gyrus in both OCD and major depression (Rosenberg et al 2004). Further study is required to determine whether riluzole preferentially targets components of the CST circuitry or has a more global effect. Additionally, the role of glutamate in the pathophysiology of mood and anxiety disorders is yet to be elucidated. The relationship between glutamate or Glx levels measured with 1H-magnetic resonance spectrometry (MRS) and the rate of glutamatergic neurotransmission is also far from clear (Seibyl et al 2001). Glutamate is present in all brain cells, where it participates in a number of cellular functions unrelated to neurotransmission. Although glutamate is the substrate for glutamatergic neurotransmission, it is not clear whether increases or decreases in glutamate levels measured by 1H-MRS reflect increased synaptic glutamate release. The extent to which synaptic or extrasynaptic glutamate contribute to the 1H-MRS glutamate signal is unknown. We hypothesize that riluzole may

reduce synaptic glutamate by attenuating elevations in extrasynaptic glutamate levels that may arise as a consequence of impairment of glial glutamate uptake (Sanacora et al 2003). Thus, the antidepressant efficacy of riluzole could be consistent with studies describing elevations (Sanacora et al 2004a) or decreases (Auer et al 2000) in cortical glutamate levels. Future studies employing 13C-MRS that can separate glial and neuronal metabolic rates will be needed to define the nature of glutamatergic disturbances in OCD and depression (Lebon et al 2002; Shen et al 1999).

The most common comorbid psychiatric illness in our study was major depressive disorder (MDD). Studies suggest that the presence of MDD in patients with OCD negatively affects treatment outcome (Foa et al 1983; Overbeck et al 2002). With recent estimates of the comorbidity between OCD and MDD ranging from 21% to 54% (Abramowitz 2004), the higher than expected percentage of study subjects with these comorbid disorders (77%) likely reflects the severity of treatment resistance in our study population. It is important to note that the efficacy of riluzole augmentation in treatment-resistant OCD remained significant even when covarying for the magnitude of antidepressant effect in our study. The clinical observation that SRIs, dopamine antagonists, and now riluzole are useful for both mood and OCD symptoms suggests a partial overlap between the pathophysiology of these disorders.

Riluzole was well tolerated in our study, and no patients discontinued treatment because of adverse effects. Riluzole is generally associated with transient elevations in LFTs; more than 50% of patients treated with riluzole experience elevations in at least one LFT measure, and approximately 2% experience LFT elevations greater than 5 times the upper limit of normal (Aventis 2004). According to the *Physician's Desk Reference*, LFTs should be monitored every month during the first 3 months of treatment, every 3 months during the remainder the first year, and then periodically. Serum LFTs should be monitored more frequently in patients who develop elevations. Riluzole therapy was discontinued for LFT elevations  $>5\times$  normal in amyotrophic lateral sclerosis (ALS) field trials. In our study, one patient demonstrated

an asymptomatic increase in ALT that exceeded 9 times normal, but ALT quickly declined on repeat testing and careful weekly monitoring. We monitored LFTs every third week and more frequently in those patients who developed significant elevations.

This study has several limitations, including its open-label design, relatively small number of patients, lack of a washout before initiation of riluzole, and concomitant treatment with standard psychotropic medications. Use of concomitant medications makes it impossible to determine whether treatment response was due to riluzole alone or its combination with other medications. This study also does not address the long-term effects of treatment with riluzole. Finally, patients were required to have had stable medications regimens for only 4 weeks before study initiation, raising the possibility that some of the treatment effect represented a delayed response to the earlier initiation of other medications. Despite these limitations, the significant improvement in Y-BOCS scores in this treatment-resistant population suggests that riluzole addition may be of practical clinical benefit in patients with OCD. Moreover, riluzole's efficacy in this study has important theoretical implications for the potential role of glutamatergic systems in treatment of anxiety and mood disorders. Future placebo-controlled studies in larger populations is warranted to follow-up on these promising preliminary findings.

*This work was supported by NARSAD Young Investigator Award 2003 (VC), the Essel Foundation (VC), the NIH Loan Repayment Program (VC), the State of Connecticut's support of the Abraham Ribicoff Research Facilities, the National Institute of Alcohol Abuse and Alcoholism (Grant No. KO5 AA 14906-01), the Department of Veteran Affairs through its support of the Alcohol Research Center and National Center for PTSD, and the General Clinical Research Center grant from the National Center of Research Resources, National Institute of Health (Grant No. M01-RR00125) awarded to Yale University School of Medicine. The authors thank the staff of the Clinical Neuroscience Research Unit of the Connecticut Mental Health Center, New Haven, Connecticut, for their contributions to the clinical management of the patients in this report. Dr. Krystal served as a scientific consultant to Aventis Pharmaceuticals, although he did not serve as a consultant on projects involving riluzole. Finally, the authors thank George R. Heninger, M.D., Neayka Sahay, M.D., Val Rosen, M.D., and Marcia Canto for their contributions to the study protocol.*

- Abramowitz JS (2004): Treatment of obsessive–compulsive disorder in patients who have comorbid major depression. *J Clin Psychol* 60:1133–1141.
- Auer DP, Putz B, Kraft E, Lipinski B, Schill J, Holsboer F (2000): Reduced glutamate in the anterior cingulate cortex in depression: An in vivo proton magnetic resonance spectroscopy study. *Biol Psychiatry* 47:305–413.
- Aventis. (2004): Rilutek. In: *Physician's Desk Reference*. Montvale, NJ: Thompson Healthcare
- Coric V, Milanovic S, Wasylinski S, Patel P, Malison R, Krystal JH (2003): Beneficial effects of the ant glutamatergic agent riluzole in a patient diagnosed

- with obsessive–compulsive disorder and major depressive disorder. *Psychopharmacology* 167:219–220.
- Baxter LR (2001): Functional imaging of brain systems mediating obsessive–compulsive disorder. In: Charney DS, Nestler EJ, Bunney BS, editors. *Neurobiology of Mental Illness*. New York: Oxford University Press, 534–547.
- Brown H, Prescott P (1999): *Applied Mixed Models in Medicine*. New York: Wiley.
- First MB, Spitzer RL, Gibbon M, Williams JBW (1997): Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). American Psychiatric Publishing, Inc.
- Foa EB, Grayson JB, Steketee GS, Doppelt HG, Turner RM, Latimer PR (1983): Success and failure in the behavioral treatment of obsessive–compulsives. *J Consult Clin Psychol* 51:287–297.
- Gueorguieva R, Krystal JH (2004): Move over ANOVA. Progress in analyzing repeated measures data and its reflection in papers. *Arch Gen Psychiatry* 61:310–317.
- Jehle T, Bauer J, Blauth E, Hummel A, Darstein M, Freiman TM, Feuerstein TJ (2000): Effects of riluzole on electrically evoked neurotransmitter release. *Br J Pharmacol* 130:1227–1234.
- Jenike MA (2004): Obsessive–compulsive disorder. *N Engl J Med* 350:259–265.
- Lebon V, Petersen KF, Cline GW, Shen J, Mason GF, Dufour S, et al (2002): Astroglial contribution to brain energy metabolism in humans revealed by <sup>13</sup>C nuclear magnetic resonance spectroscopy: elucidation of the dominant pathway for neurotransmitter glutamate repletion and measurement of astrocytic oxidative metabolism. *J Neurosci* 22:1523–1531.
- Magistretti PJ, Pellerin L, Rothman DL, Shulman RG (1999): Energy on demand. *Science* 283:496–497.
- McGrath MJ, Campbell KM, Parks CR, Burton FH (2000): Glutamatergic drugs exacerbate symptomatic behavior in a transgenic model of comorbid Tourette's syndrome and obsessive compulsive disorder. *Brain Res* 877:23–30.
- Overbeek T, Schruers K, Vermetten E, Griez E (2002): Comorbidity of obsessive–compulsive disorder and depression: Prevalence, symptom severity, and treatment effect. *J Clin Psychiatry* 63:1106–1112.
- Rosenberg DR, MacMaster FP, Keshavan MS, Fitzgerald KD, Stewart CM, Moore GJ (2000): Decrease in caudate glutamatergic concentrations in pediatric obsessive–compulsive disorder patients taking paroxetine. *J Am Acad Child Adolesc Psychiatry* 39:1096–1103.
- Rosenberg DR, Mirza Y, Russell A, Tang J, Smith JM, Banerjee SP, et al (2004): Reduced anterior cingulate glutamatergic concentrations in childhood OCD and major depression versus healthy controls. *J Am Acad Child Adolesc Psych* 43:1146–1153.
- Sanacora G, Gueorguieva R, Epperson CN, Wu Y-T, Appel M, Rothman DL, et al (2004a): Subtype specific alterations of gamma-butyric acid and glutamate in patients with major depression. *Arch Gen Psychiatry* 61:705–713.
- Sanacora G, Kendell SF, Fenton L, Coric V, Krystal JH (2004b): Riluzole augmentation for treatment-resistant depression. *Am J Psychiatry* 161:2132.
- Sanacora G, Mason G, Rothman DL, Krystal JH (2003): Clinical studies implementing glutamate neurotransmission in mood disorders. *Ann N Y Acad Sci* 1003:292–308.
- Seibyl JP, Scanley E, Krystal JH, Innis RB (2001): Neuroimaging methodologies utilizing radiotracers or nuclear magnetic resonance. In Charney DS, Nestler EJ, Bunney BS, editors. *Neurobiology of Mental Illness*. New York: Oxford University Press, 170–189.
- Shen J, Petersen KF, Behar KL, Brown P, Nixon TW, Mason GF, et al (1999): Determination of the rate of the glutamate/glutamine cycle in the human brain by in vivo <sup>13</sup>C NMR. *Proc Natl Acad Sci U S A* 96:8235–8240.
- Urbani A, Belluzzi O (2000): Riluzole inhibits the persistent sodium current in mammalian CNS neurons. *Eur J Neurosci* 12:3567–3574.
- Zarate CA, Payne JL, Quiroz J, Sporn J, Denicoff KK, Luckenbaugh D, Charney DS (2004): An open-label trial of riluzole in patients with treatment-resistant major depression. *Am J Psychiatry* 161:171–174.