Riluzole Augmentation in Treatment-Refractory Obsessive-Compulsive Disorder:
A Pilot Randomized Placebo-Controlled Trial

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ABSTRACT

Objective: Obsessive-compulsive disorder (OCD) affects approximately 2.5% of the population and is associated with significant morbidity. Many patients receive little benefit from the best available treatments, and even those who do respond often suffer from significant residual symptoms. Convergent evidence suggests that abnormalities in glutamate homeostasis and neurotransmission may contribute to OCD and that glutamate-modulating medications may be of benefit in patients whose symptoms are refractory to standard interventions. Small open-label trials of augmentation of serotonin reuptake inhibitor (SRI) pharmacotherapy with the glutamate modulator riluzole have suggested benefit in adults with refractory symptoms. We report a pilot randomized placebo-controlled trial of riluzole augmentation of ongoing SRI treatment in SRI-refractory patients.

Method: Outpatients (n = 27) and inpatients (n = 11) with *DSM-IV* OCD on stable SRI pharmacotherapy were randomized between November 2006 and December 2012 to receive riluzole 50 mg or placebo twice a day and followed for 12 weeks after a 2-week placebo lead-in phase.

Results: Riluzole was well tolerated; 1 patient experienced moderate nausea, but none discontinued treatment due to side effects. While there was nominally greater Y-BOCS improvement in the riluzole group (our primary outcome) compared to placebo, it did not reach statistical significance. In the outpatient subsample, a trend suggesting benefit from riluzole augmentation for obsessions ($P = .056$, 2-tailed, uncorrected) was found in a secondary analysis. Among outpatients, more achieved at least a partial response (> 25% improvement) with riluzole than with placebo ($P = .02$ in a secondary analysis).

Conclusions: Riluzole may be of benefit to a subset of patients. Larger samples would be required to detect effects of the order suggested by the nominal improvement in our outpatient subsample.

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Obsessive-compulsive disorder (OCD) is characterized by intrusive, distressing obsessions and ritualized compulsive behaviors that interfere with normal function.[1] It affects approximately 1.3% of the population in any given year and up to 2.7% over the course of their lifetime—an estimated 8.5 million individuals in the United States and many tens of millions worldwide.[2] Obsessive-compulsive disorder causes substantial morbidity: 60% of individuals with moderate OCD and 80% of those with severe OCD report severe role impairment in home management, work, relationships, and/or social functioning.[3]

Evidence-based treatments can benefit a majority of patients. Pharmacotherapy with serotonin reuptake inhibitors (SRIs) (the selective serotonin reuptake inhibitors [SSRIs] and clomipramine) is of proven efficacy and produces significant symptom improvement in 50%–60% of patients.[4] Specialized cognitive-behavioral therapy can be equally or more efficacious, especially when delivered by specialist providers.[5,6] When these first-line treatments fail, a variety of augmentation strategies may be of benefit.[6] Antipsychotic augmentation has demonstrated significant benefit compared to placebo in double-blind, placebo-controlled trials.[7] However, antipsychotic augmentation produces significant treatment gains in only a minority of treatment-refractory OCD patients and is associated with a substantial side-effect burden.[7] Approximately 30% of patients receive no meaningful benefit from the best available treatments, and many of those who are judged to be treatment responders continue to have significant residual symptoms. In extreme cases, profoundly affected patients turn to invasive treatments such as deep brain stimulation.[8] Remission in severe cases is rare. New treatments are urgently needed.

While first-line pharmacotherapy targets serotonergic modulatory neurotransmission, convergent evidence suggests that dysregulation of the neurotransmitter glutamate may contribute to the pathophysiology of OCD.[9] Common polymorphisms near the gene for the primary neuronal glutamate transporter, *SLC1A1*, have been associated with OCD risk in a number of studies.[10] Elevated glutamate has been reported in the cerebrospinal fluid of unmedicated adults with OCD[11,12]; some studies using magnetic resonance spectroscopy to examine brain neurotransmitters have similarly shown dysregulation of brain glutamate.[13]

These observations have motivated interest in glutamate-targeting medications as novel augmentation agents, especially in refractory disease.[9,14] Several open-label trials[15–17] of the *N*-methyl-D-aspartate (NMDA) blocker memantine and 2 recent small placebo-controlled trials[18,19] of memantine augmentation

have suggested benefit in refractory disease, although further investigation is needed to establish the benefit of this agent. The antioxidant N-acetylcysteine, which also has glutamate-modulating properties, has shown promise in case reports and a recent pilot placebo-controlled trial.[20,21] An acute challenge with the NMDA blocker ketamine, which has proven beneficial for refractory depression, may also be of benefit in OCD without comorbidity,[22] although the effect was not seen in a more clinically heterogeneous population,[23] and response may depend on comorbidities, concomitant medications, and other patient characteristics. Here, too, more work is needed. Open-label and controlled studies of indirect modulators of glutamatergic function, such as glycine,[24] sarcosine,[25] and topiramate,[26] have suggested some benefit. While none of these interventions are yet part of the standard care for OCD, these findings encourage optimism that glutamate-targeting interventions may be of benefit in refractory disease.

Open-label data also suggest benefit from the glutamate modulator riluzole in individuals with otherwise refractory OCD.[27–30] Riluzole is approved by the US Food and Drug Administration (FDA) for the treatment of amyotrophic lateral sclerosis. It has several modes of action; prominent among them, at plausible drug concentrations, are a reduction in glutamate outflow due to modulation of voltage-gated ion channels and potentiation of glial reuptake of extracellular glutamate.[29] As noted above, there is evidence for elevated brain glutamate in OCD[11,12]; this motivates the use of riluzole as an antiglutamatergic agent. In addition, limited data suggest that riluzole may be of benefit for depression and anxiety, which are commonly comorbid with OCD.[29] A recent placebo-controlled study[31] showed no benefit of riluzole in pediatric OCD, with or without comorbid autism. However, no controlled studies in adults have yet been reported.

We report the first double-blind, placebo-controlled trial of riluzole augmentation in adults with refractory OCD. We conducted a single-site pilot study of fixed-dose riluzole augmentation of stable SRI pharmacotherapy in adults to explore feasibility, estimate effect size, and potentially provide initial data as to efficacy.

Clinical Points

- Glutamate modulators are increasingly seen as a therapeutic option for obsessive-compulsive disorder (OCD) refractory to standard-of-care pharmacotherapy.
- Riluzole, a US Food and Drug Administration–approved glutamate modulator, has shown promise in open-label studies.
- Riluzole was not superior to placebo in a small double-blind study.
- There was some nominal improvement to obsessions when riluzole was added to stable serotonin reuptake inhibitor treatment, but it was not statistically significant.
- Further studies are needed to evaluate the utility of riluzole augmentation in refractory OCD.

METHOD

All study procedures were approved by the Yale University Human Investigations Committee. This trial was registered on ClinicalTrials.gov (identifier: NCT00523718).

Subjects

Subjects with SRI-refractory OCD were recruited through the Yale OCD Research Clinic (ocd.yale.edu) between November 2006 and December 2012 using print and Internet advertisements, community outreach, and physician referrals. Screening consisted of clinical interview; baseline clinical ratings (as detailed below); physical examination; blood chemistries, including liver function tests, complete blood count, and differential; and electrocardiography. Inclusion criteria were a primary *DSM-IV* diagnosis of OCD, determined by a board-certified psychiatrist and confirmed using the Structured Clinical Interview for *DSM-IV* Axis I Disorders, Clinician Version (SCID-I-CV)[32]; treatment with an SSRI or clomipramine at a stable effective dose for ≥ 8 weeks (by patient report); failure of at least 1 previous adequate-dose SSRI trial (by patient report and/or past clinical records); no changes in other medications for at least 4 weeks; use of a reliable form of birth control (for women); and documented, informed consent. *Adequate dose* of SSRIs was defined as per the current American Psychiatric Association treatment recommendations[6] or the highest tolerated dose in cases where side effects were limiting. For comparison purposes, all medication doses were converted into equivalent doses of clomipramine, using an established methodology.[33] Low-dose stable neuroleptic augmentation and benzodiazepine use were permitted to better reflect the pharmacologic profile of refractory patients in clinical practice. Ongoing psychotherapy of ≥ 12 weeks duration was permitted (analogously to the continuation of stable medication), but the initiation of new psychotherapy in outpatients was not. A single outpatient, a nonresponder in the riluzole group, was undergoing ongoing unchanged cognitive-behavioral therapy of > 2 years duration during the trial.

Exclusion criteria were prior exposure to riluzole; a clinical or SCID-I-CV diagnosis of a psychotic disorder, autism, or substance abuse or dependence within the past 6 months; a positive urine toxicology for drugs of abuse; a history of a seizure disorder or other major neurologic disease or of psychosurgery; suicidality or psychiatric instability that made participation potentially unsafe, in the evaluating psychiatrist's judgment; pregnancy or breastfeeding; any unstable medical condition; baseline transaminases > 2 × the upper limit of normal; and intellectual or language limitation that made informed consent problematic. Comorbid major depressive disorder, bipolar II disorder, anxiety disorders, hoarding, and tic disorders were permitted.

Trial Design

Subjects were treated as inpatients or outpatients; randomization was stratified across these subgroups because

inpatients received more frequent therapeutic contact that might influence response. Outpatients were evaluated on a weekly basis by an experienced nurse (S.W.) and other Clinic personnel. Inpatients were treated in the Clinical Neuroscience Research Unit of the Connecticut Mental Health Center, as in past controlled studies from our clinic[34,35]; they received limited psychotherapy from unit staff and from psychiatric residents in training. Changes in pharmacotherapy and the initiation of new psychotherapy were not permitted after initiation of the study.

Following evaluation and informed consent, all subjects began with a 2-week, single-blind, placebo lead-in phase, followed by randomization and 12 weeks of double-blind riluzole or placebo. In posttrial debriefing, no subjects expressed awareness of this initial placebo lead-in phase. Any subjects experiencing a greater than 25% improvement in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[36,37] over this 2-week placebo lead-in phase were excluded from randomization. The Y-BOCS and other symptom ratings at the end of the placebo lead-in phase were used as the baseline for analysis. Subjects were then randomized 1:1 to receive riluzole 50 mg twice a day or placebo, stratifying by inpatient versus outpatient status, using a block design. Randomization was performed by a research pharmacist using a table of random numbers; all other study personnel remained blind to treatment assignment as well as to the nature of the block randomization, which prevented guessing of group assignment during the trial. Riluzole was acquired from a commercial supplier through the Connecticut Mental Health Center research pharmacist; riluzole and placebo were prepared in identical capsules. Medication was dispensed to outpatients in 1- to 2-week supplies and to inpatients by nursing staff.

Riluzole is typically used at a dose of 50 mg twice a day. Doses of up to 100 mg twice a day have been used in some clinical studies but carry a greater side effect burden.[29] Higher doses have not been shown to be more efficacious in amyotrophic lateral sclerosis, for which riluzole is FDA approved. Our open-label pilot data suggested that the standard dose of 50 mg twice a day is efficacious and well tolerated in this population.[27] In the absence of data suggesting greater efficacy at higher doses, and given that they carry a higher side effect burden, we therefore opted for a fixed-dose regimen of 50 mg twice a day for this pilot study.

Weekly assessments consisted of the Y-BOCS, Hamilton Depression Rating Scale (HDRS; 24-item version was used for analysis),[38] and Hamilton Anxiety Rating Scale (HARS),[39] as well as clinical checks for safety and evaluation of side effects using clinical interview and the Physical Symptom Checklist.[40] Because riluzole has been associated with elevation of transaminases and, in rare cases in neurologic patients, with toxic hepatitis,[29] liver function tests were performed at baseline and at 3-week intervals after randomization. Elevation of transaminases to $>2\times$ baseline triggered weekly monitoring; elevation to $>5\times$ baseline triggered immediate termination of blinded riluzole treatment. (This threshold was not reached for any subject.) Liver function tests were monitored by a supervising psychiatrist and were not communicated to raters.

Following 12 weeks of blinded treatment, subjects and the clinical team were unblinded as each subject completed the trial. Subjects who had received riluzole were given the option of continuing open-label treatment. Subjects who had received placebo were given the option of an open-label trial. Clinical data were collected at intervals during this follow-up open-label treatment but were not systematically analyzed.

Statistical Analysis

The trial was planned to include 40 total subjects (20 in each treatment group); there were no a priori assumptions about the inpatient-outpatient breakdown of the sample. This gave us statistical power, in this pilot feasibility study, to detect large effects ($d = 0.9$ for a 2-tailed test at $\alpha = .05$; $d = 0.7$ for a 1-tailed test at $\alpha = .1$).

Data were organized using Microsoft Excel (Microsoft Corp; Redmond, Washington) and analyzed in SAS version 9.2 (SAS Institute; Cary, North Carolina) using a mixed-effects model (2-tailed, $\alpha = .05$). Treatment context (inpatient vs outpatient) was entered as an independent factor in the analysis. The primary outcome was improvement in Y-BOCS score from the prerandomization baseline to the end of blinded treatment.

Planned secondary analyses were performed on outpatient and inpatient data separately to investigate possible heterogeneity due to treatment environment and to inform future studies. Secondary outcomes were change in obsessions, change in compulsions, change in HDRS, change in HARS, and clinical response rate. Response rate was defined as a 25% improvement in Y-BOCS score for partial response and 35% improvement for full response and was analyzed using Fisher exact test.

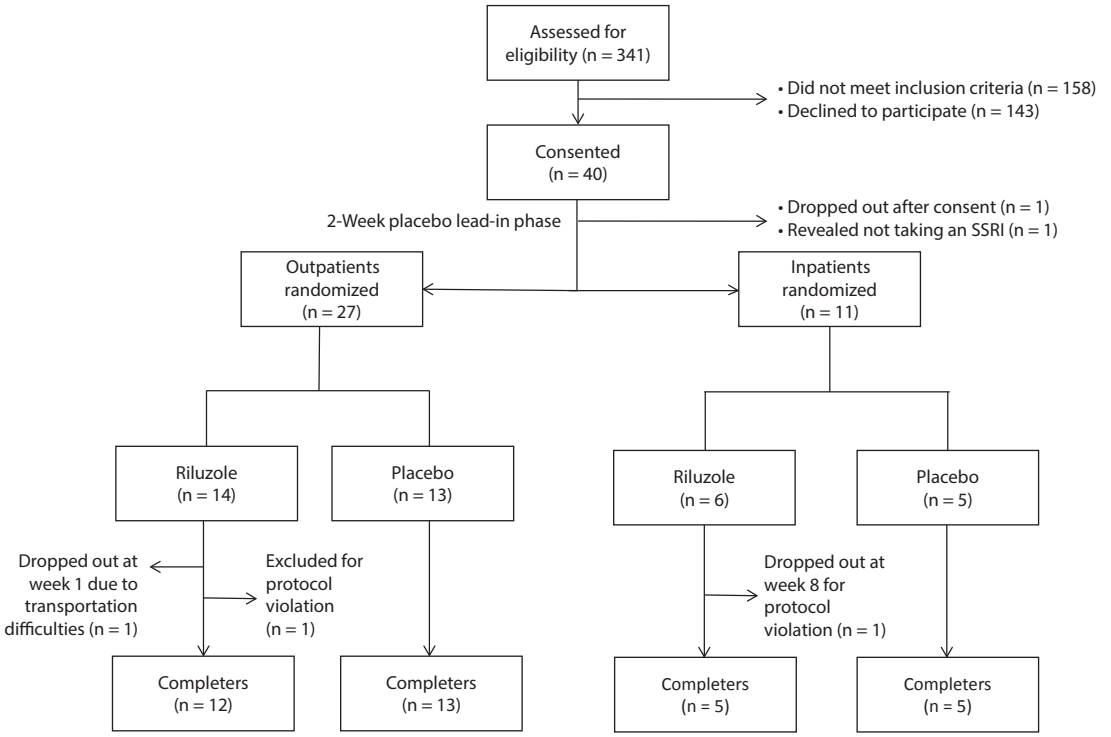
RESULTS

Subjects

The recruitment and flow of subjects is summarized in the CONSORT diagram in Figure 1. The most common reasons for nonparticipation were insufficient refractoriness (especially underdosing of SSRIs), unstable medication, and unwillingness to participate in a blinded study.

Forty subjects with treatment-refractory OCD were consented; 1 dropped out after the baseline assessment due to difficulties with transportation and interference by his symptoms with attendance at regular appointments, and a second proved not to be taking a stable SSRI. Thirty-eight subjects thus completed the single-blind placebo lead-in phase and were randomized. Symptom change over the placebo lead-in phase ranged from a 19% worsening to a 21% improvement; no subjects reached the a priori threshold of 25% improvement, which would have triggered exclusion from randomization. Randomization was stratified by

Figure 1. Patient Recruitment, Randomization, and Flow in Pilot Study



Abbreviation: SSRI = selective serotonin reuptake inhibitor.

treatment location using a block design: outpatient (14 riluzole, 13 placebo) versus inpatient (6 riluzole, 5 placebo). Concomitant medications, comorbidities, and other characteristics are summarized in Table 1.

One randomized patient was excluded from analysis due to a protocol violation (he was taking variable amounts of pain medication throughout the study period without informing study personnel). The decision to exclude this individual from analysis was made before unblinding; he had been assigned to the riluzole group. His Y-BOCS score was unchanged from baseline at the time of exclusion. With this exclusion, a total of 37 subjects (19 riluzole, 18 placebo) were analyzed. Two other early dropouts occurred in the riluzole group and were included in analysis. One occurred 1 week after randomization (due to difficulty in transporting himself to weekly clinic appointments) and the second 8 weeks after randomization (due to a protocol violation; he stopped taking his study medications for a period of several days). There were no dropouts in the placebo group.

Y-BOCS Improvement and Response

All clinical outcome measures and statistical analyses are presented in Table 2. Y-BOCS change from baseline (mean ± SD) was −11% ± 14% in the placebo group versus −15% ± 26% in the riluzole group at week 12. This nominal difference did not approach statistical significance in a mixed model analysis of all data, with treatment location (inpatient vs outpatient) included as an independent factor (Table 2; Figure 2A).

At week 12, there were 5 of 19 partial responders in the riluzole group by the a priori definition of a 25% improvement from baseline Y-BOCS (4 outpatients, 1 inpatient, using last observation carried forward for dropouts) and 2 of 18 partial responders in the placebo group (0 outpatient, 2 inpatients). This difference did not reach statistical significance in the overall sample ($\chi^2_1 = 1.39$, $P = .24$) but did in the outpatient subsample ($\chi^2_1 = 4.36$, $P = .023$). By a more stringent criterion for full response of 35% improvement from baseline and a final Y-BOCS score of ≤ 16, there were 3 responders in the riluzole group (2 outpatients, 1 inpatient) and 1 in the placebo group (an inpatient). Examination of the 4 outpatient responders (by the 25% improvement criterion) did not reveal obvious clinical correlates of responder status. All 4 were women, but they varied in age (30–62 years), comorbidity (3 depressed, 3 with social anxiety disorder, 2 with past ethanol abuse), concurrent medication, and type of primary OCD symptom (1 primary checking, 1 primary contamination, 1 primary symmetry, 1 mixed).

Planned stratified analysis by treatment location showed a nominal benefit from riluzole treatment in the outpatients, though it was not statistically significant. In outpatients (12 riluzole, 13 placebo), there was a −8% ± 11% change in Y-BOCS (mean ± SD) in the placebo group and a −16% ± 26% change in the riluzole group. The time × treatment interaction in this subsample approached significance ($t_{307} = -1.57$, $P = .12$, 2-tailed, uncorrected). This suggests an effect size of $d = 0.45$; if corroborated by a larger study, this would correspond to a medium effect.

Table 1. Clinical and Demographic Characteristics of Study Subjects[a]

Characteristic	Riluzole (n = 19)	Placebo (n = 18)	Comparison
Sex, n			
Male	11	9	
Female	8	9	
Age, y	41.5 ± 3.2	36.4 ± 3.1	NS
Education, y	14.6 ± 0.5	14.3 ± 0.6	NS
Race			
White	19	16	
African American		2	
Onset of OCD			
Minor symptoms	10.8 ± 1.7	11.6 ± 1.4	NS
Major symptoms	21.2 ± 2.8	20.2 ± 2.8	NS
Diagnosis	27.8 ± 3.6	19.5 ± 2.3	$P = .07$
MDD, n (%)			
Lifetime	15 (79)	12 (66)	
Current	10 (53)	9 (50)	
Tics, n (%)	6 (32)	4 (22)	
Anxiety disorders, n (%)			
Panic disorder	3 (16)	4 (28)	
Social anxiety disorder	8 (42)	4 (22)	
Generalized anxiety disorder	2 (11)	2 (11)	
PTSD	1 (5)	0	
Specific phobia	2 (11)	2 (11)	
Y-BOCS baseline score	29.6 ± 1.2	29.1 ± 1.3	NS
Obsessions	15.4 ± 0.5	14.8 ± 0.8	NS
Compulsions	14.7 ± 0.7	15.0 ± 0.6	NS
Percent change during lead-in	−2.2% ± 2.7%	−4.9 % ± 2.4%	NS
HDRS baseline score	12.7 ± 1.6	13.1 ± 1.4	NS
HARS baseline score	16.2 ± 1.7	15.9 ± 1.5	NS
SRI (clomipramine equivalents), mg	270 ± 18	258 ± 22	NS
Fluoxetine	5	6	
Citalopram	2	3	
Escitalopram	4		
Sertraline	2	2	
Fluvoxamine	4	3	
Paroxetine			
Clomipramine	2	2	
Venlafaxine		2	
Other medication			
Neuroleptic	5	5	
Benzodiazepine	4	6	
Other sleep aid	1	4	
Topiramate		2	
Lithium		1	
Gabapentin	1		
Lamotrigine	1		
N-acetylcysteine	1		
Buspirone	2	1	
Memantine		1	
Stimulant	1	1	
Baseline liver function test			
AST/SGOT	22.0 ± 2.0	20.7 ± 1.8	NS
ALT/SGPT	30.8 ± 4.7	22.9 ± 4.0	NS
Week 9 liver function test			
AST/SGOT	27.9 ± 3.7	24.5 ± 4.0	NS
ALT/SGPT	48.1 ± 8.5	30.1 ± 5.7	$P = .12$

[a]Unless noted otherwise, all values are mean ± standard error of the mean.
Abbreviations: ALT = alanine transaminase, AST = aspartate aminotransferase, HARS = Hamilton Anxiety Rating Scale, HDRS = Hamilton Depression Rating Scale, MDD = major depressive disorder, NS = not significant, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder, SGOT = serum glutamic-oxaloacetic transaminase, SGPT = serum glutamic pyruvic transaminase, SRI = serotonin reuptake inhibitor, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Secondary Measures

We performed planned secondary analyses of obsessions (Y-BOCS-obsessions) and compulsions (Y-BOCS-compulsions). The change from baseline in obsessions (Y-BOCS-obsessions) was −7% ± 13% in the placebo group (mean ± SD) and −13% ± 29% in the riluzole group, suggesting an effect size of $d = 0.30$ (Table 2). In the outpatient subsample, the change in Y-BOCS-obsessions was −3% ± 9% in the placebo group and −18.5% ± 27% in the riluzole group, with a suggested an effect size of 0.80; in a mixed model analysis, the time × group interaction approached significance ($t_{307} = -1.92$; $P = .056$, 2-tailed, uncorrected).

The change from baseline in compulsions (Y-BOCS-compulsions) was −14% ± 18% in the placebo group and −15% ± 28% in the riluzole group. There was a main effect of time in the overall sample and in both outpatient and inpatient subsamples, but no effects of treatment or interactions (Table 2).

Depression and anxiety scores were low to moderate at baseline and showed no substantial change across the 12 weeks of treatment. The HDRS and HARS both nominally increased in both placebo- and riluzole-treated groups, with no significant differences between groups. Interestingly, there was a significant effect of treatment environment (inpatient vs outpatient) on HARS scores, irrespective of treatment assignment (outpatient: 13.4 ± 6.1 at randomization, 12.4 ± 5.6 at end point; inpatient: 16.8 ± 5.0 at randomization, 18.5 ± 6.2 at end point; main effect of treatment venue, $t_{433} = -2.17$, $P = .03$). The effect of treatment venue, which was included as an independent factor in all analyses, did not approach significance for any other outcome variable.

Side Effects and Adverse Events

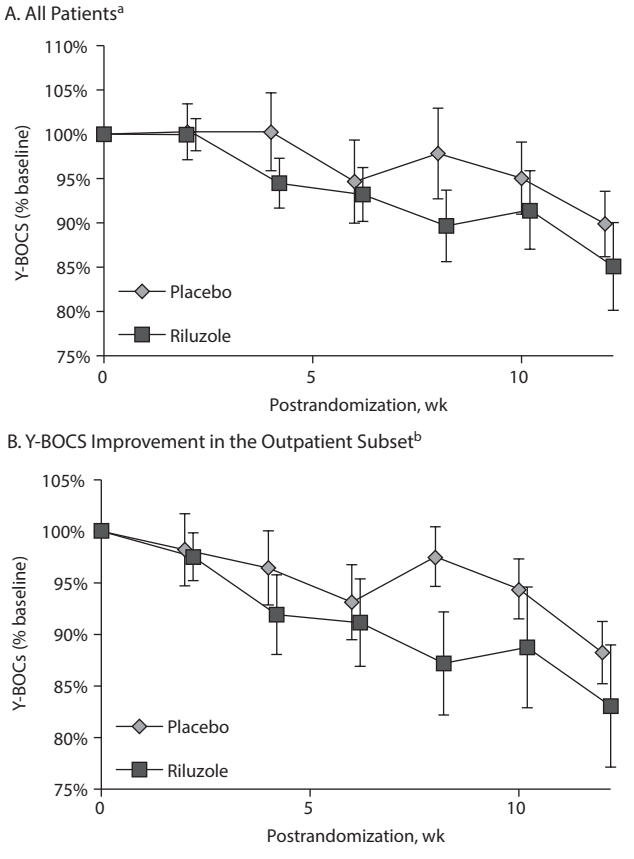
One subject who was randomized to receive placebo experienced a period of feeling "unsafe" and passively suicidal; this had occurred previously. It dissipated after several hours of support from clinic personnel; he continued the study through completion, and there was no recurrence. A second subject with a history of depression, PTSD, alcohol dependence (in remission), and back pain from a work-related accident was assigned to the riluzole group. He was later found to have been taking variable, high amounts of prescription opiates, prescribed for pain control by an outside clinician, throughout the study. At 10 weeks after randomization he developed a confusional state while at home and took an overdose of these prescribed narcotics in an effort to control his anxiety; medical hospitalization and treatment in an intensive care unit were required. He was withdrawn from the study; once it became clear that he had been taking variable, high doses of narcotic pain relievers without revealing this to study personnel, his data were retrospectively excluded, prior to analysis, as noted above. At the time of the

Table 2. Mixed-Model Statistical Analyses of Clinical Outcome Measures[a]

Measure	Placebo Baseline	Riluzole Baseline	Placebo Change	Riluzole Change	Effect Size (treatment)	*df*	Time		Treatment		Time × Treatment	
							t	*P*	*t*	*P*	*t*	*P*
Y-BOCS												
Overall	29.6 ± 5.4	29.1 ± 5.9	−11% ± 14%	−15% ± 26%	0.17	433	−3.4	.0007	0.01	> .5	−0.71	.48
Outpatient	28.5 ± 5.1	30.6 ± 4.3	−8% ± 11%	−16% ± 26%	0.45	307	−2.20	.03	1.12	.27	−1.57	.12
Inpatient	32.4 ± 5.7	26.0 ± 7.7	−17% ± 20%	−12% ± 27%	…	124	−2.77	.006	−1.25	.21	0.91	.36
Y-BOCS-obsessions												
Overall	15.4 ± 2.6	15.3 ± 2.1	−7% ± 13%	−13% ± 29%	0.30	433	−2.42	.016	0.47	> .5	−0.99	.32
Outpatient	14.8 ± 2.2	15.7 ± 1.8	−3% ± 9%	−18.5% ± 27%	0.80	307	−1.37	.17	1.08	.3	−1.92	.056
Inpatient	16.8 ± 3.3	14.5 ± 2.5	−19% ± 17%	−2% ± 33%	…	135	−2.39	.02	−0.62	> .5	1.1	.27
Y-BOCS-compulsions												
Overall	15.1 ± 2.4	14.6 ± 3.0	−14% ± 18%	−15% ± 28%	…	433	−3.63	.0003	−0.31	> .5	−0.38	> .5
Outpatient	14.8 ± 2.3	14.9 ± 2.6	−13% ± 16%	−13% ± 30%	…	307	−2.52	.01	0.95	.34	−0.95	.34
Inpatient	15.6 ± 2.8	13.8 ± 4.1	−15% ± 24%	−18% ± 23%	…	124	−2.73	.007	−1.34	.18	0.62	> .5
HDRS-24												
Overall	12.9 ± 6.3	11.7 ± 5.6	10% ± 64%	2% ± 46%	…	444	−0.68	.5	−0.15	> .5	−0.38	> .5
Outpatient	11.8 ± 6.5	11.5 ± 6.6	16% ± 70%	−6% ± 36%	…	307	−0.62	> .5	0.34	> .5	−0.73	.47
Inpatient	15.8 ± 5.5	12.2 ± 3.3	−3.5% ± 46%	21% ± 65%	…	124	−0.28	> .5	−1.01	.31	0.41	> .5
HARS												
Overall	14.3 ± 5.7	13.7 ± 5.1	6% ± 43%	3% ± 31%	…	433	−1.48	.14	−0.40	> .5	0.80	.42
Outpatient	12.5 ± 4.9	13.0 ± 5.3	7% ± 50%	−1% ± 37%	…	307	−1.62	.11	0.14	.9	0.39	> .5
Inpatient	19.2 ± 5.3	15.0 ± 4.8	2% ± 24%	13% ± 5%	…	124	−0.23	> .5	−1.04	.3	0.8	.43

[a]All values are mean ± SD. The primary outcome measures were Y-BOCS improvement in the overall sample and the outpatient subsample; other analyses are exploratory.
Abbreviations: HARS = Hamilton Anxiety Rating Scale, HDRS-24 = 24-item Hamilton Depression Rating Scale, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.
Symbol: … = effect size of $d < 0.1$.

Figure 2. Y-BOCS Across 12 Weeks of Double-Blind Augmentation With Riluzole (50 mg/d), Following a 2-Week, Single-Blind, Placebo Lead-In Phase



[a]There was a significant main effect of time ($P = .0007$), but no significant effect of treatment group or treatment × time interaction (see Table 2).
[b]There was again a main effect of time ($P = .03$), but the effect of treatment and treatment × time interaction did not reach significance (see Table 2).
Abbreviation: Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

overdose, he had not exhibited any change in Y-BOCS score (34 at both randomization and dropout); HDRS and HARS scores had improved (HDRS: 30 to 18; HARS: 32 to 28). This adverse event was categorized as severe but more likely related to his variable use of narcotic pain medications than to his participation in the study.

Physical Side Effects

Overall, riluzole was well tolerated. No subjects dropped out due to physical side effects. Physical side effects were assessed at baseline and at weekly assessments by clinical interview and the Physical Symptom Checklist. Data from the Physical Symptom Checklist were not available for the first 4 patients randomized; the n for this analysis is therefore 16 for riluzole and 17 for placebo. Two measured symptoms were more frequent in riluzole-treated patients: nausea (3 riluzole vs 1 placebo) and poor coordination (3 riluzole vs 1 placebo). One subject, an inpatient randomized to receive riluzole, had significant nausea with a few episodes of emesis; moderate nausea persisted throughout the study period, though the subject chose not to drop out before study completion. In contrast, many measured physical symptoms were reported more frequently in placebo-treated than in riluzole-treated patients (eg, constipation: 1 riluzole vs 6 placebo; poor memory: 1 riluzole vs 6 placebo; pounding heartbeat: 0 riluzole vs 3 placebo), and many others did not differ between groups. There were no respiratory side effects and no pancreatitis, by clinical criteria.

Liver Function Tests

Liver function test abnormalities have been associated with riluzole use.[29] We measured aspartate aminotransferase (AST) (serum glutamic-oxaloacetic transaminase) and alanine transaminase (ALT) (serum glutamic pyruvic

transaminase) at baseline and every 3 weeks during double-blind treatment with riluzole. No statistically significant change in AST was seen over the course of riluzole treatment. Alanine transaminase increased in the riluzole group, reaching a maximum at week 9, at which point the difference between groups approached significance (2-tailed *t* test: $P = .07$; see Table 1). Four subjects in the riluzole-treated group and 1 in the placebo group showed elevation of 1 transaminase to $> 2 \times$ baseline at some point during the trial. Our protocol set a priori criteria for discontinuation of treatment due to asymptomatic transaminitis (1 measure $> 5 \times$ upper limit of normal); no subjects met these criteria at any point during the study.

DISCUSSION

There has been substantial recent interest in the possible role for glutamate dysregulation in the pathophysiology of OCD and the potential benefit of glutamate-modulating medications in the treatment of refractory disease.[9,41,42] In particular, a number of small, open-label studies and a few pilot controlled trials have suggested benefit from riluzole, memantine, *N*-acetylcysteine, topiramate, glycine, and sarcosine.[15–18,24–28,30] A pair of open-label trials[27,30] from our group have suggested that riluzole augmentation of SSRI (or clomipramine) treatment may be of benefit in patients whose symptoms have been profoundly refractory to standard treatment modalities. More recently, a controlled trial[31] in children with OCD, with or without comorbid autism, failed to show any benefit. However, controlled data in adults have been lacking.

We present the first placebo-controlled, double-blind trial of riluzole augmentation of SSRI treatment in adults with refractory OCD. There was a nominal improvement in Y-BOCS score in the riluzole-treated group, but it did not reach statistical significance in a mixed model analysis. Planned secondary analyses showed greater evidence for benefit, though still only at trend level, in the outpatient subgroup and when only obsessions were considered.

The size and methodology of our study limited our ability to detect small or medium effects of riluzole with statistical significance. Power may have been further reduced by the inclusion of both inpatients and outpatients; a trend suggesting benefit from riluzole was seen only in the outpatient subsample. To identify a true positive finding with the effect size of $d = 0.45$ suggested by the outpatient subsample with 80% power, using a 2-tailed test, would require 100 subjects in each treatment arm. While such effects may be clinically significant, our single-site pilot study was not powered to detect them.

Additional variability may have been contributed to our sample by the relatively broad inclusion criteria. While comorbid autism, psychosis, and substance abuse were excluded, comorbid major depressive disorder and anxiety disorders, as well as Tourette syndrome, hoarding disorder, and other OCD-related conditions, were permitted. Additionally, a relatively broad range of medications frequently seen in clinical practice was permitted, as was ongoing long-established psychotherapy; these included augmentation treatment with neuroleptics, benzodiazepines, and other glutamate-modulating agents. These choices were made so as to reflect in our study the treatment-refractory population as it is seen in clinical practice, but increased heterogeneity in the sample may have muddied modest treatment effects.

Initial SSRI treatment in OCD has a large effect size.[4] However, smaller effects are to be expected in the treatment-refractory population. Direct comparisons to previous studies are of limited utility because of the very different patient populations being examined: most studies of SSRI pharmacotherapy have examined treatment-naive patients, whereas we were selecting for a treatment-refractory population that had already failed 2 attempts at standard-of-care pharmacotherapy.

This pilot study was of fixed dose and limited duration. These design choices were derived from our earlier open-label pilot data.[27] Higher doses of riluzole produce more side effects without clinical benefit in amyotrophic lateral sclerosis.[29] However, it may be that higher doses would enhance clinical benefit in OCD.[30] Similarly, 12 weeks of treatment is typically sufficient to see a clinical response in treatment studies of OCD, and our pilot data suggested that any benefit of riluzole augmentation should be apparent over this time,[27] but greater benefit may emerge with longer follow-up. Future studies of riluzole augmentation should systematically explore higher doses and longer periods of treatment.

A recently reported study of riluzole augmentation in pediatric OCD, with or without comorbid autism, found no evidence for benefit, even at trend level.[31] The age at onset of major symptoms in our sample was over 20 years (see Table 1), although such retrospective numbers are prone to recall bias. It is increasingly appreciated that childhood-onset and adult-onset OCD may be genetically and etiologically distinct.[43,44] It may be that certain treatments will prove to be more efficacious in one or the other of these populations. Due to the small size of our sample and the imprecision of retrospective report of symptom onset, a stratified analysis based on onset was not possible in our sample; this should be addressed in future studies.

Outpatient Versus Inpatient Treatment

There was nominal benefit from riluzole in the outpatient subsample (though at $P = .12$ it did not reach statistical significance), whereas there was none in the inpatient subsample. This may be because of the presence of unique confounds in the inpatient subsample, including both therapeutic structure and symptom triggers in the inpatient milieu. Anxiety, as measured by the HARS, was higher in the inpatient subsample; other clinical measures did not differ between inpatients and outpatients.

Obsessions Versus Compulsions

Exploratory analysis suggests greater benefit from riluzole augmentation in obsessions, at trend level,

than in compulsions. Compulsions (as measured by the Y-BOCS-compulsions) improved over the course of the trial, but there was no difference in them between riluzole and placebo groups either in the overall sample or in the outpatient subsample. In contrast, there was a nominally greater improvement in obsessions (Y-BOCS-obsessions) in riluzole-treated patients, both in the overall sample and in the 2 subsamples. In the outpatient subsample, this approached significance ($P = .056$, 2-tailed, uncorrected), although this must be interpreted with caution given the exploratory nature of this secondary analysis.

Depression and Anxiety

Riluzole monotherapy and augmentation have been suggested as a potential treatment for both depression[45–47] and generalized anxiety disorder.[48] These effects have yet to be validated in controlled studies, although controlled trials of riluzole augmentation in refractory unipolar (ClinicalTrials.gov identifiers: NCT01703039 and NCT01204918) and bipolar depression (ClinicalTrials.gov identifier: NCT00054704) are underway.

However, baseline HDRS and HARS scores were substantially lower in this cohort than in open-label studies that have specifically focused on those diagnoses. This limits our ability to see any benefit from riluzole treatment on anxiety and depression. With that caveat, we found no trend toward an improvement in depression or anxiety symptoms. It may be that any benefit of riluzole in clinical depression and anxiety does not generalize to subclinical levels of symptomatology, or the effect size for such relatively mild symptoms may simply be insufficient for any trend to be detectable in a sample of this size.

Mechanism of Action

Riluzole can modulate glutamate in the central nervous system through several mechanisms.[29,49] In neurons,[49] it reduces glutamate release through its effects on voltage-gated sodium channels[50]—a mechanism that overlaps that of lamotrigine—and potentiates calcium-activated sodium channels. Riluzole also enhances glutamate reuptake by glia by up-regulating the principle glial glutamate transporter, GLT-1 (also called excitatory amino acid transporter 1 [EAAT1]), thus potentially modulating glutamate homeostasis.[29,51–53] In vivo, magnetic resonance spectroscopy data suggest that riluzole can acutely increase the rate of glutamate turnover,[54] consistent with a potentiation of reuptake. Interestingly, various antidepressants have been shown to induce GLT-1 and other markers of glutamatergic neurotransmission, at least in animals,[55–57] suggesting a possible convergence of mechanisms.

It remains unclear how such effects might interact with the pathophysiologic abnormalities underlying OCD. Mutations in the gene encoding the primary neuronal glutamate transporter, excitatory amino-acid transporter 3 (EAAT3), have been associated with OCD in several studies, suggesting a possible causal role of dysregulated glutamate homeostasis.[10] The hypomorphic nature of some of these mutations[58,59] and the observation of increased glutamate in the cerebrospinal fluid of unmedicated patients,[11,12] along with the results of a subset of magnetic resonance spectroscopy measures of glutamate in individuals with OCD,[13] suggest a state of localized or general glutamate excess. Normalization of this state through increased glial reuptake of glutamate represents a potential therapeutic mechanism of riluzole.[29]

Limitations

The primary limitation of our study, which was intended to probe feasibility and tolerability rather than to provide definitive evidence of efficacy, was the small sample size. With 20 subjects per group, we had only 23% power to detect medium effects of $d = 0.4$. Heterogeneity introduced by the inclusion of both inpatients and outpatients and by the fairly broad inclusion criteria (in terms of concomitant medications, ongoing established psychotherapy, and comorbid diagnoses) may have reduced power by increasing variability. Additionally, the inclusion of subjects with current or past treatment with glutamate-modulating agents may have enhanced the refractoriness of these subjects to riluzole (although other glutamate modulators such as lamotrigine and topiramate are thought to have distinct mechanisms of action).

CONCLUSION

To the best of our knowledge, we describe the first placebo-controlled, double-blind feasibility study of riluzole augmentation in adults with a major psychiatric disorder. This pilot study did not demonstrate efficacy in OCD but was not powered to detect small to medium effects. There were trends suggestive of benefit, especially in the outpatient subsample and especially in measures of obsessions (with little evidence of benefit to compulsions). We are unable to determine whether the failure to demonstrate statistically significant effects represents a true lack of efficacy or a type II error due to insufficient statistical power. Riluzole was well tolerated in this population. Transient elevations in ALT were noted but were self-limited and clinically insignificant in all cases.

Convergent evidence has suggested a role for glutamate dysregulation in OCD,[9] but the details of any such role remain obscure. Better-powered controlled studies of glutamate-modulating medications are essential to determine the role for such agents, if any, in the pharmacotherapy of refractory disease.

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Drug names: citalopram (Celexa and others), clomipramine (Anafranil and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), gabapentin (Neurontin, Gralise, and others), ketamine (Ketalar and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), memantine (Namenda and others), paroxetine (Paxil, Pexeva, and others), riluzole (Rilutek and others), sertraline (Zoloft and others), topiramate (Topamax and others), venlafaxine (Effexor and others).

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Avanier, Bristol-Myers Squibb, Eli Lilly, Hoffman-La Roche, Merck, Naurex, Noven, and Takeda, and has received research support from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Hoffman-La Roche, Merck, Naurex, and Servier. **Dr Coric** is now a full-time employee of Bristol-Myers Squibb, is a paid consultant to New Haven Forensics Consultants and the Center for Research and Development, and is a shareholder for Bristol-Myers Squibb. **Drs Coric** and **Sanacora** are originators on the patent Glutamate Agents in the Treatment of Mental Disorders (USPTO no. 11/399188; April 5, 2006) and have a financial interest in Biohaven Pharmaceutical Holding Company, a privately held company that has licensed this intellectual property. **Drs Bloch** and **Kelmendi**, **Mss Wasylink** and **Billingslea**, and **Messrs Simpson** and **Jakubovski** have no real or apparent conflict of interest to declare.

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