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An Open-Label Trial of Riluzole, a Glutamate Antagonist, in Children with Treatment-Resistant Obsessive-Compulsive Disorder

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ABSTRACT

Background: **Obsessive-compulsive disorder (OCD) in childhood is often refractory to treatment. Riluzole, a glutamate antagonist, has theoretical support as an alternative pharmacological treatment and has demonstrated possible benefit in some open-label trials in adults with OCD.**

Methods: **Six subjects, ages 8–16 years, were enrolled in a 12-week open-label trial of riluzole for OCD symptoms that had resisted prior treatments. OCD symptoms and adverse effects of drug were monitored.**

Results: **Four of 6 subjects had clear benefit, with reduction of more than 46% (39% overall) on Children's Yale-Brown Obsessive-Compulsive Scale, and "Much Improved" or "Very Much Improved" on the Clinical Global Impressions–Improvement scale. Two subjects had no clinically meaningful change in symptom severity by 12 weeks, but 1 subject improved thereafter. There were no adverse effects of drug sufficient to cause discontinuation or reduction of dose. All subjects elected to continue riluzole after the 12-week trial.**

Conclusions: **Riluzole may be beneficial for treatment-resistant OCD in young subjects and seems well tolerated. A placebo-controlled trial of the drug is planned.**

INTRODUCTION

Dysfunction of orbitofrontal-striatal-thalamocortical circuitry has been postulated in the etiology of obsessive-compulsive disorder (OCD) (Saxena and Rauch 2000). Glutamate plays a key role at several points in this circuit (Fig. 1), and glutamatergic excess (relative or absolute) could contribute to symptomatology. Evidence for a glutamatergic excess in the pathophysiology of OCD is found in a recent report in which cerebrospinal fluid had significantly higher glutamate levels in drug-naïve adult subjects with clinically significant OCD compared to controls (Chakrabarty et al. 2005). Particularly relevant for childhood-onset OCD may be the recent findings of a significant association of a gene that codes for an ex-

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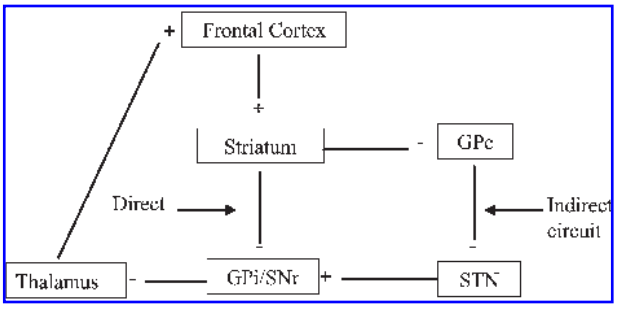

FIG. 1. OCD, glutamate, and the orbital-frontal-striatal-thalamocortical circuit. In this postulated model for OCD, glutamatergic excess in the orbital frontal cortex causes increased excitation of the striatum, which increases its inhibitory output to the globus pallidus interna (GPi) and substantia nigra (pars reticulata) (SNr). This, in turn, causes a decrease in its inhibitory output to the thalamus, resulting in a release of thalamic excitatory output to the frontal cortex. In essence, a positive feedback loop is established, leading to repetitive thoughts (obsessions) and behaviors (compulsions). The globus pallidus externa (GPe) and subthalamic nucleus (STN) may constitute an external loop contributing to a steady state of excitation/inhibition in this model.

citatory amino acid carrier, with early-onset OCD in male (but not female) subjects (Arnold et al. 2006; Dickel et al. 2006). (Glutamate is the primary excitatory amino acid neurotransmitter in the brain. A defect in production of its carrier could result in excess synaptic glutamate.)

The effect in OCD of the serotonin reuptake inhibitors (SSRIs) might also be explained through a glutamate mechanism. The orbitofrontal cortex has projections to dorsal raphe nuclei, which in turn send serotonergic input to the striatum. There are also direct orbitofrontal cortical glutamate projections to the striatum, and glutamate causes striatal release and turnover of serotonin and regulation of serotonin receptor numbers. A rat model of OCD has been used to demonstrate these relationships (Joel et al. 2005). Reduction of glutamate at points in the relevant circuit could restore what may normally be a fine balance of neurotransmission maintaining a steady state.

Riluzole (Rilutek®) is a member of the benzothiazole class, with a good safety record and extensive experience in the treatment of amyotrophic lateral sclerosis. The most common reported adverse effect is transient elevation of liver transaminases (Lacomblez et al. 2002; Pongratz et al. 2000; Zoing et al. 2004). Riluzole's ability to function as a relative glutamate antagonist suggests it might have therapeutic effects in OCD by reducing the orbitofrontal cortical (excitatory) output to the striatum, which would reduce the striatal inhibition of the globus pallidus and substantia nigra and allow greater inhibition of the thalamus and less cortical excitation. McGrath and colleagues have postulated effectiveness of similar compounds in a mouse model of Tourette's disorder and OCD (McGrath et al. 2000).

Riluzole was used successfully to augment other pharmacotherapy in an adult patient who had failed treatment with prior regimens for his severe and refractory OCD and major depressive disorder (Coric et al. 2003). There have also been case reports of the benefit of riluzole for a patient with chronic skin-picking as well as an eating disorder (Sasso et al. 2006) and in a patient with self-injurious behavior (Pittenger et al. 2005). In an open-label trial for treatment-resistant OCD, 13 adult patients received 50 mg of riluzole twice a day as an augmenting agent. Five were categorized as treatment responders, with a Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score less than 16, and 35% or greater reduction from baseline score, as well as clinical consensus improvement. The study was extended from 6 to 9 weeks and then to 12 weeks as subjects continued to demonstrate improvement. The drug was well tolerated, with no serious adverse effects noted (Coric et al. 2005).

The SSRIs are frequently ineffective in childhood OCD. In an optimized research setting, response to an SSRI alone was 39% (March et al. 2004). And in a naturalistic setting, when there were co-morbid conditions, the rate was 67% (Masi et al. 2005). There would appear to be a place, then, for alternative pharmacologic treatments. To our knowledge, there have been no previous reports of the use of riluzole for the treatment of children and adolescents with OCD. We report the results of riluzole treatment of 6 children with refractory OCD during a 12-week open-label trial.

MATERIALS AND METHODS

The Institutional Review Board of the National Institute of Mental Health (NIMH) ap-

proved the protocol. Six subjects, ages 8.3–16.4 (mean 14.4) years, gave informed assent, and their parents consented to study participation. All subjects had at least moderately severe symptoms of OCD with Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) scores of 25–31 (mean = 29)]. All had had symptoms present for months or years and had failed to respond to treatment with at least one antiobsessional medication (SSRIs), at a usually effective dose for a time generally sufficient to demonstrate symptom relief. Some had also had trials of exposure and response prevention, a cognitive-behavioral therapy (CBT) effective in OCD (March et al. 1994; March 1995). In all cases, the local providers were contacted for corroboration that there had been at least one trial of an SSRI that had been of sufficient length and dose, and that the patient was still significantly distressed and impaired (Table 1). (These providers agreed to remain active in the patients' care throughout the study.) The subjects continued previously prescribed medications throughout the study period, but did not initiate new medications, nor did they engage in CBT. Two subjects were taking no other medicines at baseline.

Primary outcome measures were the C-YBOCS and Clinical Global Impressions–Improvement (CGI-I) score. Treatment response was defined as a 30% or greater reduction in obsessive-compulsive symptom severity from baseline to the end of the trial period, as well as by a score of "Much Improved" or "Very Much Improved" on CGI-I.

Riluzole was administered in 10-mg capsules, prepared by the National Institutes of Health (NIH) Clinical Center Pharmacy from the 50-mg tablets, which are the only dosage form available from the manufacturer. The protocol allowed a maximum dose of 120 mg daily.

Subjects returned to the NIH clinic at week 1 and then every 2 weeks for assessment of OCD symptoms and adverse events, as well as for laboratory studies. Between on-site visits, there were phone calls to review symptom status and to assess adverse effects. Riluzole was continued after the end of the 12 weeks if desired, and dose could continue to be adjusted.

RESULTS

Details about co-morbid psychiatric diagnoses (determined by psychiatric evaluation and semistructured interview), as well as about prior treatments are provided in Table 1.

The dose of riluzole was increased by 10 mg every few days. In two cases, the dose was increased to the maximum allowed in the protocol (120 mg daily) because significant OCD symptoms were persistent and the medicine was well tolerated. All subjects took at least 50 mg of riluzole twice a day by the end of the study, except for subject 1, who did not achieve that dose until after 12 weeks. This subject experienced drowsiness, but was taking other medications that might have been responsible, although the drowsiness seemed worse after riluzole was added. As a result, riluzole was increased only slowly during the 12 weeks. But after other medicines were discontinued, drowsiness resolved, and riluzole was increased. Subjects 2 and 3 took 120 mg daily by end of 12 weeks. Subjects 4, 5, and 6 took 100 mg by end of 12 weeks. The average dose by 12 weeks was 101 mg of riluzole daily.

Subject 5 did not quite meet our criteria for treatment response in that he was not "Very Much Improved," according to CGI measure by 12 weeks, but by all other measures there was no question of the change, and by week 16 he had become entirely asymptomatic. Subjects 3 and 6 did not meet criteria for response by the end of 12 weeks. However, both subjects elected to continue riluzole after the end of the study. Neither of these subjects has had any adverse effects from riluzole, and based on the experience of Subject 5 and that of the adult subjects, there is reason to prolong the trial for a time.

Table 2 shows results for each subject at the end of the 12 weeks of the study (as well as at most recent visit). Descriptive statistics are included in the table. Some important findings are worth emphasizing. At baseline, each subject had distressing and highly impairing OCD symptoms despite previous treatment regimens, which, as required by the protocol, were of sufficient duration and dose to have been expected to be of benefit. After this trial, 2 patients (subjects 4 and 5) became almost com-

TABLE 1. COMORBID DIAGNOSES, MEDICATION AND THERAPY HISTORY FOR PATIENTS

			Medications and therapy		
Subject no.	*Baseline date*	*KSADS diagnoses at baseline*	*Before baseline*	*During 12 weeks*	*After trial*
1*	1/20/06	1. OCD	**Age 8:** fluoxetine not effective. Later: multiple other meds.; inadequate effect. **Age 9:** started CBT; OCD worsened. For at least one month before baseline: clomipramine 100mg bid; clonazepam 0.5mg q.am, 1mg q.pm; fluvoxamine 25mg bid. CBT continued up to protocol baseline (1/20/06).	**Baseline to Week 8:** clomipramine 100mg bid; clonazepam 0.5mg q.am, 1mg q.pm; fluoxetine 25mg bid. **Week 8:** clomipramine 50mg bid; clonazepam 1mg HS; fluvoxamine 25mg bid **Week 12:** clomipramine 25mg q.am, 50mg q.pm; clonazepam 1mg HS; fluvoxamine 25mg bid.	**Week 14:** clomipramine 25mg q.am, 20mg q.pm; clonazepam 1mg HS; fluvoxamine 25mg bid. Sometime soon thereafter, subject stopped all medicines except study drug.
2	5/18/06	1. OCD; 2. Major Depressive Disorder; 3. Separation Anxiety Disorder	Only briefly engaged in CBT, derived no benefit. Has tried (with limited or no success): fluvoxamine, fluoxetine, sertraline, quetiapine, buspirone, and others. Meds at screening visit (4/13/06): multivitamin; escitalopram 20mg QD, for at least last 6 months (i.e., since 9/05); fexofenadine prn.	**Continued:** escitalopram 20mg QD; multivitamin. Stopped fexofenadine for the 12 weeks. **6/28/06:** taking cephalexin and acetaminophen prn. **8/16/06:** took cephalexin for 8 days previous, with no regularity.	Stopped escitalopram on 2/23/07
3	7/27/06	1. OCD; 2. Major Depressive Disorder, past; 3. Tourette's Disorder	**Jan. '05:** sudden onset tics, OCD. Hospitalized Nov. 2-14 '05: citalopram & pimozide tried; stopped for untoward side effects. **At baseline:** sertraline 100mg, 1-1/2 QD; ziprasidone 40mg bid; clonazepam 2mg q.am, 3 mg HS; amoxicillin 250mg bid; melatonin 3mg HS; omega-3 caps, 1200mg QD; fexofenadine 60mg bid; albuterol prn; ibuprofen 800 mg QD prn. No CBT or other therapy.	**9/9/06:** stopped AM dose of clonazepam (now just 3mg QD). **9/10/06:** ziprasidone reduced to 20mg **9/23/06:** ziprasidone stopped. **9/27/06:** ziprasidone resumed, 20mg QD. **9/28/06:** ziprasidone increased to 20mg. **9/29/06:** sertraline increased to 150mg; melatonin increased to 6mg HS. **10/1/07:** ziprasidone increased to 40mg TID.	Most recently: ziprasidone 40 mg qd; clonazepam 1 mg q.am and 2 mg HS; sertraline 150 mg.

4	8/11/06	1. OCD; 2. Major Depressive Disorder; 3. Separation Anxiety Disorder; 4. Transient Tic Disorder	CBT never worked. **Sept. '05:** fluoxetine 20mg. 1/20/06: stopped fluoxetine; started sertraline on that date, but stopped by 6/12/06. **At baseline:** no meds. except loratidine.	loratidine throughout.	loratidine prn.
5	9/21/06	1. OCD; 2. Major Depressive Disorder; 3. Separation Anxiety Disorder; 4. Generalized Anxiety Disorder	"For a long time," "for a period of up to 2 years": tried fluoxetine; fluvoxamine 450mg QD; risperidone; aripiprazole. For at least 6 months before baseline: stopped all meds. Had tried CBT in past: didn't work for him.	None.	None.
6	10/20/06	1. OCD; 2. Major Depressive Disorder (at least 3 episodes); 3. Generalized Anxiety Disorder; 4. Oppositional Defiant Disorder; 5. Tourette's Disorder	**Sept. '06:** started CBT. **Oct. '05:** started sertraline at 50mg; was taking 200mg by study baseline. loratidine 10mg QD; mometasone prn.	sertraline 200 mg; loratidine prn.	sertraline 200 mg; loratidine.

*Note that for Patient 1, the study period was extended three months past the 12-week mark, to August 2006. KSADS (Children's Schedule for Affective Disorders and Schizophrenia).

OCD = obsessive compulsive disorder; CBT = cognitive behavioral therapy.

TABLE 2. PATIENT CHARACTERISTICS, DEPENDENT-VARIABLE MEASURES, AND STUDY DRUG DOSES

Subject number	Baseline age (years)	Sex	CY-BOCS				Global CGI-Severity (CGI-Improvement)			Riluzole (per day, mg)	
			Baseline	12 weeks	Change (%)	Latest rating	Baseline	12 weeks	Latest rating	At 12 weeks	Latest visit
1	14.5	M	30	19	37	18	6	4 (2)	3 (1)	70	100
2	16.4	M	28	20	29	14	6	4 (2)	3 (2)	120	100
3	16.7	F	30	26	13	19	5	4 (3)	4 (3)	120	150
4	8.3	M	29	10	65	10	5	3 (2)	3 (2)	100	100
5	15.8	M	25	10	60	0	4	4 (4)	2 (2)	100	100
6	14.9	M	31	21	32	24	6	6 (4)	4 (3)	100	200
Means (standard deviations)	14.4 (3.1)		28.8 (2.1)	17.7 (6.4)	39.3 (19.7)	14.2 (8.4)	5.3 (0.8)	4.2 (1.0)	3.2 (0.8)	101.7 (18.3)	125.0 (41.8)

Abbreviations: CY-BOCS = Children's Yale-Brown Obsessive-Compulsive Scale; CGI = Clinical Global Improvement Scale–Severity and Improvement.

pletely symptom-free, taking only riluzole. Subject 1, who had been taking three other drugs (with significant adverse effects), stopped those medications when his symptoms abated during riluzole therapy; nevertheless, his symptoms have fallen nearly into the subclinical range. A fourth patient (subject 2) also met our criteria for treatment response, and his symptoms have not worsened despite stopping all prior medicines.

There were no serious adverse events among the six young people. One (subject 4) had transient elevations of liver enzymes. Lactate dehydrogenase was slightly elevated (237 U/L) (normal = 113–226) even prior to study drug, rose to a high of 263, and then fell to normal (213), even though riluzole was continued. Aspartate (normal = 9–34) and alanine (normal = 6–41) transaminases also rose slightly to highs of 49 and 50, respectively, and then fell to normal (30 and 18, respectively) despite continuing riluzole dose unchanged. In a second patient (subject 2), aspartate aminotransferase (AST) levels rose from 27 at baseline to 47, and alanine aminotransferase (ALT) levels rose from 39 to 75. This patient continues riluzole and is being followed very carefully. The protocol stipulated that drug must be stopped or reduced if liver enzymes double from predrug baseline. One subject reported excessive drowsiness during riluzole administration, but this appeared to be related to other medications, because it abated when those medications were discontinued. Another patient had a single episode of abdominal pain, apparently unrelated to riluzole therapy.

DISCUSSION

This is the first report of the use of riluzole for OCD in pediatric subjects. In this open-label study, 4 subjects were considered "responders" and have elected to continue taking riluzole and to discontinue other medications. Two other subjects did not have significant symptom improvement by the end of the 12 weeks of the study, but have elected to remain on riluzole and to extend the trial period. Of the two nonresponders, one was female—of possible importance, given the recent finding of a gene associated with OCD and excitatory amino acid carrier, noted above.

This study suffers from the small sample size and from the limitations of any open-label trial, such as the inability to distinguish the source of improvement during the trial. A placebo-controlled trial will address these weaknesses and is underway at the NIMH.

CONCLUSION

Riluzole may be of benefit in childhood OCD and was well tolerated in these 6 patients.

DISCLOSURE

Drs. Grant and Swedo and Ms. Lougee and Mr. Hirschtritt have no conflicts of interest or financial ties to disclose.

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