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Efficacy of glutamate modulators in tic suppression: A double-blind, randomized control trial of D-serine and riluzole in Tourette Syndrome

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Abstract

Background—It has been hypothesized that glutamatergic transmission may be altered in Tourette syndrome (TS). In this study, we explored the efficacy of a glutamate agonist (D-serine) and antagonist (riluzole) as tic-suppressing agents in children with TS.

Methods—We performed a parallel 3-arm, 8-week, double-blind, randomized placebo-controlled treatment study in children with TS. Each child received 6 weeks of treatment with D-serine (maximum dose 30 mg/kg/day), riluzole (maximum dose 200 mg/day), or placebo, followed by a 2-week taper. The primary outcome measure was effective tic suppression as determined by the differences in the Yale Global Tic Severity Scale score (YGTSS); specifically, the Total Tic score (TTS) and the combined score (TTS + global impairment) between treatment arms after 6 weeks of treatment. Mann-Whitney U tests were performed to analyze differences between each group and the placebo group.

Results—Twenty-four patients (males = 21, ages 9-18) enrolled in the study and one patient dropped out prior to completion. Combined YGTSS and TTS scores improved in all groups. The 6-week mean percent improvement of the riluzole (n=10), D-serine (n=9), and placebo (n=5) groups in the combined YGTSS were 43.7, 39.5, and 30.2 percent and for TTS were 38.0, 25.0, and 34.0 percent, respectively. There were no significant differences in YGTSS or TTS, respectively, between the riluzole and placebo ($p = 0.35, 0.85$) or D-serine and placebo ($p = 0.50, 0.69$) groups.

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Conclusion—Tics diminished by comparable percentages in the riluzole, D-serine, and placebo groups. These preliminary data suggest that D-serine and riluzole are not effective in tic suppression.

Keywords

tourette syndrome; tics; d-serine; riluzole; glutamate

Introduction

Tourette syndrome (TS) is a chronic neuropsychiatric condition characterized by the presence of fluctuating motor and vocal tics. Tics vary widely in severity and many patients require treatment to improve associated psychosocial, physical, and functional difficulties. While current treatment strategies offer benefit to many patients, newer medicinal approaches for tic suppression are needed given inadequate control and adverse side effects with current therapies.^{1,2}

The primary site of the brain abnormality in TS is unknown. Based on both direct and indirect evidence, the cortico-striatal-thalamo-cortical (CSTC) circuits that run from the frontal cortex to the putamen and then back to the cortex via the thalamus are likely involved. The presence of a variety of different neurotransmitters within this CSTC circuitry suggests the possibility that multiple neurotransmitters may be involved in the pathophysiology of TS. While dopamine dysfunction has long been considered the primary abnormality, other neurotransmitters could also be implicated.³ One potential candidate is the excitatory neurotransmitter glutamate.

Modulators of glutamatergic neurotransmission have been considered as potential therapeutic agents in TS based upon several lines of evidence including glutamate's essential role in CSTC circuits and proposed interactions between the glutamatergic and dopaminergic neurotransmitter systems in the prefrontal cortex, midbrain, and striatum.⁴⁻⁷ Additional support for a possible role of the glutamatergic system in TS includes familial genetic studies and reduced post-mortem levels of glutamate in the globus pallidus and substantia nigra pars reticulata.⁸⁻¹¹

It remains unclear, however, if neurochemical data support a hyper- or hypoglutamatergic condition in TS. Mechanistically, one could hypothesize a rationale to support the benefit of either a hyper- or hypo-glutamatergic state. For example, increased afferent excitation of the striatum could result from increased stimulation of glutamatergic pyramidal neurons in the pre-frontal cortex, resulting in a hyperkinetic disorder such as tics. In this scenario, a glutamate antagonist may offer benefit. Alternatively, given postmortem evidence of reduced glutamate levels in the globus pallidus and substantia nigra, a glutamate agonist may be beneficial.^{12,13} Given this mechanistic uncertainty, this study sought to investigate two glutamate modulators, the glutamate agonist D-serine and the glutamate antagonist riluzole.

Serine is an endogenous ligand at the glycine site of the NMDA receptor complex, an ionotropic glutamate receptor.^{14,15} It has been suggested that D-serine may also act as a

gliotransmitter that mediates interactions between glia and neurons.^{16,17} In addition, recent studies have shown that neurons synthesize and secrete D-serine.¹⁸ D-cycloserine, a related compound with an additional nitrogen, is thought to be a partial agonist at the NMDA receptor. Attempts to treat patients with schizophrenia and obsessive compulsive disorder (OCD) using d-cycloserine have produced variable results.¹⁹⁻²⁵

Riluzole's mechanism is complex and not fully understood. It is thought to inhibit the presynaptic release of glutamate by blocking voltage-gated sodium channels.²⁶ Riluzole is FDA-approved for use in amyotrophic lateral sclerosis and is currently being studied in a number of neuropsychiatric disorders, including childhood OCD.²⁷

In this study, we aimed to explore the efficacy of D-serine and riluzole, each compared to placebo, in children with TS.

Methods

Participants

All patients seen in clinic with a tic disorder were assessed for eligibility. Patients were included if they [a] met criteria for TS as defined by the TS Classification Study Group, which includes onset before 18 years, multiple involuntary motor tics, one or more vocal tics, a waxing and waning course, the gradual replacement of old symptoms with new ones, the presence of tics for more than one year, the absence of other medical explanations for tics, and the observation of tics by a reliable examiner. [b] Age 8-17 years, either gender; [c] Observable tics, achieving a minimum score > 22 on the Total Tic score of the Yale Global Tic Severity Scale (YGTSS); [d] Tic symptoms severe enough to warrant therapy; [e] The concurrent use of other tic-suppressing medications was permitted if the subject had been on a stable dose for more than three weeks and agreed to maintain a constant dosage throughout the study; [f] Tics were not controlled with current medication or individuals were tic-suppressing drug naïve.²⁸

Exclusion criteria included: [a] secondary tics; [b] significant medical illness; [c] current major depression, generalized anxiety disorder, separation anxiety disorder, psychotic symptoms (based on clinical evaluation), pervasive developmental disorder, autism, intellectual disability (I.Q. less than 70), anorexia/bulimia, or substance abuse. [d] pregnancy; [e] hypersensitivity to D-serine or riluzole; [f] baseline weight of less than 33 kilograms; [g] abnormal laboratory values on baseline laboratory testing.

Study design and procedures

This was a parallel 3-arm, 8-week double-blind randomized placebo-controlled treatment study in 24 children with TS. Each child received 6 weeks of treatment with a glutamate antagonist (riluzole), glutamate agonist (D-serine), or placebo, followed by a 2-week taper. A post-intervention assessment was also performed at the end of week 8. Approval was obtained through the Johns Hopkins Institutional Review Board. Patients were randomized by the study pharmacist using a computer-generated 2:1 (glutamate modulating drug: placebo) scheme to assign patients to a study medication: riluzole, D-serine, or placebo. Medications, packaged in look-alike capsules, were distributed by the study pharmacist. The

research pharmacist retained the medication codes until the completion of the study. The investigators, study coordinator, and patient/parent were not aware of the treatment assignment. A drug safety monitoring board monitored side effects and assisted in any decisions to withdraw a participant.

Medication administration

Dosage increases occurred during treatment weeks 1, 2, 3, and 4, as determined by the treating physician (HS). The starting dose of riluzole was 50 mg for one week; administered as one capsule every morning. If needed, as determined by the treating physician, the dose was increased weekly by 50 mg and given as a twice daily dosage. The maximum dose used was 200 mg/day (administered as 2 capsules twice daily).

The starting dose of D-serine was approximately 7 mg/kg/day, given in 250 mg or 500 mg capsules. This was titrated weekly to a dose of approximately 30 mg/kg/day, which was also used as the maximum dose. Immediately following the treatment phase (week 6), medication was tapered over a 2 week period, with a reduction of one capsule every other day.

Evaluations

All patients underwent a screening visit that included determination of eligibility criteria and rating scales for *tics* (YGTSS, Clinical Global Impression-TS (CGI-I)) and Patient Global Impression of Improvement (PGI-I), *obsessive-compulsive problems*, (Child) Yale-Brown Obsessive Compulsive Scale ((C)Y-BOCS); *attention deficit hyperactivity disorder*, DuPaul ADHD Rating Scale, *depression*, Depression Inventory-Short Version (DI-S); and *anxiety*, the Multidimensional Anxiety Scale (MAS-C).²⁹⁻³⁸

Screening labs included urinalysis, comprehensive metabolic panel, complete blood count, serine level, and urine b-HCG in female patients. Alternating telephone (HS) and clinic (MG) evaluations were performed weekly by blinded study physicians. Telephone evaluations occurred at the end of weeks 1, 3, and 5 (± 2 days) and included discussions of clinical response, side effects, drug compliance, and medication adjustment. Subjects were evaluated in clinic at baseline at the end of weeks 2, 4, and 6. Direct clinical evaluations included YGTSS, (C)Y-BOCS, CGI-I and PGI-I. Evaluation at each clinic visit additionally included vital signs, weight, and an assessment of side effects and discussions of medication adjustment. Additional scales, including the CYBOCS, DuPaul ADHD Rating Scale, DI-S, and MAS-C were administered at baseline and end of week 6. Post-intervention assessment was performed at week 8 (± 2 days, HS).

Outcome and safety measures

The YGTSS is a semi-structured clinical interview designed to measure current tic severity. This validated scale is considered the preferred standardized method to rate tic severity.³⁹⁻⁴⁰ The primary outcome measure was effective tic suppression as determined by the individual percent change in YGTSS Total Tic scores (TTS) and combined YGTSS (TTS + impairment) scores at baseline and after 6 weeks of treatment. Secondary outcome measures included the CGI-I and PGI-I.

Safety measures included an expanded Pittsburgh Side Effect Scale modified to include side effects of riluzole and D-serine; blood and urine testing performed at baseline and at each clinic visit; and changes in the (C)Y-BOCS, DuPaul ADHD rating scale, DI-S, and MAS-C.

Statistical Analysis

All analyses were performed using an intent-to-treat model. Summaries of percent change in YGTSS and TTS were calculated as the means of individual percent changes. Mann-Whitney U tests were performed to analyze differences in outcome measures and quantitative variables between groups. Spearman correlations were calculated between the change in levels of blood serine and TTS and YGTSS for the D-serine group. Power calculations estimated that approximately 19 subjects per group would provide a desired power of 0.9 to detect a difference of 4.2 points in the mean 6-week change in YGTSS Total Tic Score between comparisons of the treatment arms, using a two-tailed t-test and a 5% level of significance.

Results

Thirty-nine patients were screened for eligibility. Twenty-four patients were enrolled in the study; divided into the 3 arms of those receiving riluzole (n=9), D-serine (n=10), and placebo (n=5). Twenty-three children completed the study. The single child who discontinued the study completed through week 4 and was in the placebo group (Table 1). The average final daily dose was 3.5 mg/kg/day in the riluzole group and 26.8 mg/kg/day in the D-serine group.

All groups, including placebo, had an improvement in tic suppression as measured by TTS, with a mean percent improvement from baseline to week 6 of 38.0, 25.0, and 34.0 percent in the riluzole, D-serine, and placebo groups, respectively (Table 2). There were no significant differences in percent improvement in TTS between riluzole and placebo groups ($p = 0.85$) or between D-serine and placebo ($p = 0.69$) at week 6 (Figure 1).

In the YGTSS at week 6, all groups improved, with a mean percent improvement from baseline to week 6 of 43.7, 39.5, and 30.2 percent in the riluzole, D-serine, and placebo group, respectively. There were no significant differences in percent improvement in YGTSS between riluzole versus placebo groups ($p = 0.35$) or between D-serine versus placebo groups ($p = 0.50$) at week 6 (Figure 2).

In the secondary outcome CGI-I, evaluation showed no significant difference between the riluzole and placebo and the D-serine ($p = 0.22$) and placebo groups at week 6 ($p = 0.75$).

Blood serine was significantly elevated in all patients in the D-serine group at week 6 as compared to baseline ($p = 0.04$). A Spearman correlation analysis did not show any significant correlation between blood serine level and TTS or YGTSS scores (data not shown).

There were no significant differences in co-morbidities (as measured by the CYBOCS, MAS-C, DuPaul ADHD rating scale) between groups with drugs at week 6 compared to the placebo group (Table 3). Patients in the D-serine group had a 41.7 percent improvement

(range: +100% to -11%) in (C)Y-BOCs scores, as compared to a -1.0 percent improvement (range: +20% to -25%) seen in the placebo group ($p = 0.08$).

There were no significant differences in percent improvement in TTS between children who were on other medications at the start of the study and those who were not. Riluzole and D-serine were well-tolerated, with no serious adverse events reported. The most common side effects reported included gastrointestinal upset ($n=5$), fatigue ($n=4$), diarrhea ($n=4$), irritability or moodiness ($n=4$), and lightheadedness or dizziness ($n=4$); none of which required medical intervention or discontinuation of treatment (Table 4).

Discussion

The goal of this study was to determine the therapeutic efficacy of a glutamate agonist and antagonist in TS, given ongoing interest in glutamate neurotransmission in this disorder. In this randomized, double-blind placebo-controlled study, patients in the D-serine, riluzole, and placebo groups experienced a comparable reduction in tics. The tic suppression that occurred in all groups was similar to that seen in commonly used therapies.⁴¹ Both riluzole and D-serine were well tolerated, with no significant adverse events reported.

The placebo effect has been described recently in tic disorders by Cubo et. al, who demonstrated that the magnitude of improvement resulting from placebo effect was relatively small (0.16 for all participants, 0.18 for children), but clinically relevant.⁴² The etiology of this effect remains unclear; with suggestions including observer bias, inaccuracy of self-assessment of tic severity, or the fluctuating nature of tics. The magnitude of improvement seen in our small placebo group was larger than that typically described. These data emphasize that attempts to reduce the number of controls to enhance the proportion of subjects receiving drug may be shortsighted.

Unfortunately, this study failed to clearly define whether glutamatergic modulators are beneficial as tic suppressing agents. Had the placebo effect been equivalent to published studies, a strong recommendation for additional studies would be appropriate. In terms of effects on other co-morbidities, D-serine reduced obsessive compulsive behaviors as compared to both riluzole and placebo. While the data are mixed, there is some suggestion that D-cycloserine, a partial agonist, augments cognitive behavioral therapy in difficult-to-treat patients with pediatric OCD.^{23,43,44}

Our work was clearly limited by its small sample size and recruitment did not reach the goals outlined in initial power calculations. As such, it was inadequately powered to detect small significant differences between subgroups. Further, the treatment duration was relatively brief, making it difficult to discern treatment effect from the natural, fluctuating course of tics. While many of the baseline characteristics of the group were similar, there were a disproportionate number of females in the D-serine group. The improvement seen with both glutamate agonists and antagonists highlights our incomplete understanding of glutamatergic neurotransmission in tic disorders. Further study with a larger population and a longer treatment period is needed to better interpret these findings.

Despite these limitations, this study is novel in its attempt to characterize the efficacy of glutamate agonists and antagonists in TS. These results do not negate the hypothesis that glutamate may play an important role in the pathophysiology of tics. It is our hope that these data prompt further study into the role of glutamatergic modulation in TS and other tic disorders.

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Figure 1.
Boxplots of individual percent improvement in TTS from baseline to week 6.

Figure 2.
Boxplots of individual percent improvement in YGTSS from baseline to week 6.

Table 1

Clinical Trial Flow Diagram

Table 2

Tic Baseline to 6-week Data

Groups	Gender (male, females)	Age (mean, range)	TTS Mean $\pm$ SD				YGTSS Combined Score Mean $\pm$ SD			
			Baseline	6 Week	Mean % Change	P-value	Baseline	6 Week	Mean % Change	P-value
Placebo										
Total (n=5):	(5, 0)	12.6, 10-16	31.4 $\pm$ 7.1	21.2 $\pm$ 8.4	34.0%		64.6 $\pm$ 15.6	45.2 $\pm$ 15.3	30.2%	
Other Meds Yes	(2, 0)	11.0, 10-12	24.5 $\pm$ 4.9	16 $\pm$ 7.1	36.3%		52.5 $\pm$ 9.2	41 $\pm$ 14.1	23.1%	
No	(3, 0)	13.6, 10-16	36 $\pm$ 3.0	24.7 $\pm$ 8.3	32.4%		72.7 $\pm$ 14.2	48 $\pm$ 18.3	35.0%	
Riluzole										
Total (n=10):	(10, 0)	13.1, 11-17	29.9 $\pm$ 7.8	19.4 $\pm$ 11.5	38.0%		61.9 $\pm$ 16.7	38.4 $\pm$ 23.8	43.7%	
Other Meds Yes	(7, 0)	13.1, 12-15	33 $\pm$ 6.8	22.6 $\pm$ 11.1	34.3%		68.7 $\pm$ 13.4	44 $\pm$ 23.9	40.2%	
No	(3, 0)	13.0, 11-17	22.7 $\pm$ 5.0	12 $\pm$ 10.5	48.2%		46 $\pm$ 13.1	25.3 $\pm$ 21.5	51.9%	
<i>Riluzole vs Placebo:</i>						0.85				0.35
D-serine										
Total (n=9):	(6, 3)	14.4, 9-18	27.8 $\pm$ 4.6	21.6 $\pm$ 10.6	25.0%		58.6 $\pm$ 8.3	36.6 $\pm$ 20.2	39.5%	
Other Meds Yes	(4, 3)	13.9, 9-17	28.1 $\pm$ 4.5	23.1 $\pm$ 10.7	19.4%		60.6 $\pm$ 6.4	39.6 $\pm$ 19.6	35.2%	
No	(2, 0)	16.0, 14-18	26.5 $\pm$ 6.4	16 $\pm$ 11.3	43.1%		51.5 $\pm$ 13.4	26 $\pm$ 25.5	54.4%	
<i>D-Serine vs Placebo:</i>						0.69				0.5

* Mean % Change was calculated based on the mean of individual percent changes.

Table 3

Co-Morbidity Baseline to 6 week Data

Scales	Placebo (n=4)			p-value	Riluzole (n=10)			p-value	D-serine (n=9)			p-value
	Baseline	6 Week	Mean % Change		Baseline	6 Week	Mean % Change		Baseline	6 Week	Mean % Change	
DuPaul ADHD												
Inattentive	12.3	10.8	16.6%		14.3	13.2	5.9%	0.25	12.1	11.0	6.3%	0.27
H-I	11.3	7.0	30.8%		11.3	10.6	7.8%	0.39	9.9	7.8	19.3%	0.68
Combined	23.5	17.8	24.6%		25.6	23.8	3.1%	0.19	22.0	18.8	13.6%	0.35
MACS	62.0	55.8	10.1%		48.2	51.5	13.9%	0.4	42.9	41.6	1.5%	0.5
CY-BOCS	8.0	8.8	1.0%		7.3	5.5	24.4%	0.71	11.0	5.1	41.9%	0.08

* p-value comparison between drug group and placebo.

Table 4

Side Effects

Side Effect	Placebo (n, %)	Riluzole (n, %)	D-serine (n, %)
Fatigue	0	2, 20%	2, 22%
Gastrointestinal upset	0	2, 20%	3, 33%
Diarrhea	1, 20%	2, 20%	1, 11%
Irritability, moodiness	0	1, 10%	3, 33%
Lightheadedness, dizziness	1, 20%	2, 20%	1, 11%
Headache	1, 20%	2, 20%	0
Sleeplessness	0	1, 10%	1, 11%