



Effect of L1-79 on Core Symptoms of Autism Spectrum Disorder: A Case Series

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ABSTRACT

Purpose: This study examines the effects of the tyrosine hydroxylase inhibitor L1-79, a racemic formulation of α -methylparatyrosine, in patients with autism spectrum disorder (ASD) in a prospective case series. The L-isomer formulation of α -methylparatyrosine, metyrosine, is approved for the management of patients with pheochromocytoma.

Methods: Six male and 2 female patients aged 2.75 to 24 years with ASD were treated for 8 weeks at L1-79 doses ranging from 90 to 400 mg thrice daily. Assessments at weekly intervals included the Aberrant Behavior Checklist–Community (ABC-C), Connor's Parent Rating Scale (CPRS), and Clinical Global Impressions (CGI) scale. The Autism Diagnostic Observation Schedule (ADOS) was administered at baseline and week 10.

Findings: The ABC-C and CPRS scores improved between baseline and end of study for 7 of 8 participants; most participants' assessment scores decreased. At week 8, the CGI efficacy index was 05 for 6 of 8 participants, indicating modest improvement with at least partial resolution of symptoms and no medication adverse effects, and 09 for 2 participants, indicating minimal improvement and no change in status or care needs, without adverse effects. The mean ADOS scores improved by $\geq 31\%$ for 4 of the 6 participants tested, with 1 patient experiencing a 47% improvement. Seven of the 8 participants previously taking psychotropic medications were stable without their legacy medications while receiving L1-79, and 1 patient resumed a single legacy medication at a lower dose. Three adverse events were reported; symptoms were mild and resolved without change in therapy.

Implications: These results suggest L1-79 may be a tolerable and effective treatment for the core symptoms of ASD, which must be confirmed with double-blind

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Key words: α -methylparatyrosine, autism spectrum disorder, catecholaminergic inhibition, core symptoms of autism spectrum disorder, L1-79.

INTRODUCTION

The prevalence of autism spectrum disorder (ASD) has increased substantially since the 1990s and currently affects approximately 3.5 million individuals in the United States, although recent estimates suggest a leveling off (which may be attributable to changes in epidemiologic methods).¹ The estimated cost of care is \$2.4 million per individual during the lifetime, including education, special housing, medical care, and caregiver productivity loss.^{2,3} In the United States, no medications have been approved for the core symptoms of ASD, and only aripiprazole and risperidone are approved for the management of irritability or agitation. These agents have potentially serious adverse effects, including tardive dyskinesia and weight gain; the latter increases patients' risk of metabolic syndrome and other metabolic abnormalities.⁴

The core symptoms of ASD include communication difficulties; trouble understanding relationships; restricted and repetitive behavior, interests, or activities; and difficulties in social interactions.⁵ These impairments appear to be mediated by catecholaminergic neurotransmission in the sympathetic nervous system, limbic system, hypothalamus, and brainstem via nutrient-sensing mechanisms that reticulate throughout the central

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nervous system (CNS) to the cortex, basal ganglia, and other structures.⁶ The conversion of tyrosine to dihydroxyphenylalanine by tyrosine hydroxylase is the first and rate-limiting step in the biosynthesis of catecholamines, including dopamine, norepinephrine, and epinephrine. The tyrosine hydroxylase inhibitor L1-79, a racemic formulation of α -methylparatyrosine, is currently under evaluation as a treatment for the core symptoms of ASD (NCT02947048). The L-isomer of α -methylparatyrosine, metyrosine*, is approved for the management of patients with pheochromocytoma. Because metyrosine is an approved agent, and the US Food and Drug Administration 505(b)(2) guidance states that any stereoisomer of an approved agent can be considered to be the same agent, this investigator-initiated trial was predicated on using the D,L-isomer as an unapproved use of an approved agent.⁷ At approved doses of 1000 to 4000 mg/d, metyrosine is associated with sedation, gastrointestinal effects, tremor, and, at higher doses, trismus, extrapyramidal signs, and other motor disturbances.⁸ L1-79, which is administered at a fraction of the metyrosine dosage, is currently used in a polytherapeutic regimen under clinical development for the treatment of various tumor types (NCT03512756; Tyme Technologies Inc, New York, New York). Hyperpigmentation and rash were the most common drug-related adverse events observed with this polytherapy regimen that included L1-79; all adverse events in the trial were mild to moderate in intensity. No serious adverse events or deaths were attributed to study drug, and no adverse events led to discontinued use of the study drug.⁹

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In light of the tolerability of L1-79 when used in a polytherapeutic regimen in heavily pretreated patients with stage 4 cancer,⁹ we believed this agent would be tolerable to use in otherwise healthy individuals with ASD. Given the potential effects on ASD pathophysiology, we designed a prospective case series to examine the effects of low doses of L1-79 on ASD.

METHODS

Case Series Design

We initiated a prospective case series in which L1-79 was administered to patients with ASD in an unblinded

fashion to observe its effects on ASD symptoms. Participants were recruited from 1 pediatric (Sea Girt Pediatrics, Sea Girt, New Jersey) and 1 child psychiatric practice (Bartky Healthcare Center, Livingston, New Jersey) in the United States. A central institutional review board (Schulman Institutional Review Board, No. 201605120) approved the protocol and consent form on April 31, 2016. All participants provided written informed consent before the initiation of treatment with L1-79. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article. Consent was provided by the legal guardians or proxies of children younger than 18 years and adult study participants unable to care for themselves.

Participants

All case series participants were healthy individuals of both sexes between 2.75 and 24 years of age with a diagnosis of ASD according to criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (DSM-5).⁵ The diagnosis was also confirmed by the Autism Diagnostic Observation Schedule (ADOS), which was assessed by an independent test-certified clinical psychologist.^{10,11} To be included, participants needed to be able to cooperate with study staff and caregivers needed to be able to comply with the study protocol. Exclusion criteria included a history of ASD-associated congenital or systemic conditions, such as fragile X syndrome, Retts syndrome, tuberous sclerosis, or phenylketonuria; epilepsy; use of complementary alternative medications; abnormal hepatic or renal function tests; any unexplained laboratory value; pregnancy or nursing; and a positive test result for any drug of abuse, including opiates.

Procedures

To assess the effects of L1-79 as a single agent on ASD symptoms without the confounding effects of concomitant psychotropic medications, per the protocol, individuals taking such medications at screening underwent a 2-week washout before starting use of L1-79, with the exception of participant 5, who continued her legacy medication at a reduced dose. Participants received L1-79 three times daily for 8 weeks. The starting dose of 90 mg

thrice daily was recommended by the inventor of L1-79 (Steve Hoffman, personal communication, October 2015), based on his experience, including studies of L1-79 as a component of a multidrug regimen for various tumor types.⁹ Dosage was adjusted in an escalating manner based on tolerability and patient response. Treatment adherence was assessed by recording unused medication in the drug log.

Assessments

Assessments included the ADOS, Aberrant Behavior Checklist–Community (ABC-C), the Connor's Parent Rating Scale (CPRS), and the Clinical Global Impressions (CGI) scale.^{10–15} The ADOS is a validated scale used for diagnosis, and the choice of ADOS module used is a function of presence or absence of language and participant age, and scores indicative of ASD vary according to module and age of individual being tested.^{10,11} Assessments were conducted by the same independent certified clinical psychologist for all tests in all patients. The ABC-C is a validated 58-item behavior rating scale used to measure behavior problems across 5 subscales. Items are rated on a 4-point Likert scale (ranging from 0 [not at all a problem] to 3 [the problem is severe in degree]), with higher scores indicating more severe problems.^{12,16} CGI determinations are based on test scores, clinical observations, and parent reports, and this instrument includes an efficacy index that incorporates both efficacy and adverse effects into a grading scale of 01 to 16, in which higher numbers indicate lower efficacy and/or greater impact of adverse effects (Table I).^{14,15} The full range of potential adverse effects and adverse events were reviewed in detail with the parents by the investigator and considered in the calculation of the CGI. Assessments were administered at each weekly visit unless logistical or participant-specific factors prevented administration of a test. Qualitative reports from parents and/or legal guardians were collected, and participants' use of concomitant medications was also documented. The ADOS was administered at week 1 and week 10.

Results of assessments were documented on an individual basis. Safety information, including physical examinations with vital signs and the adverse event monitoring data, was collected at each study visit. Adverse events were assessed by asking

Table I. Clinical Global Impressions scale. Reproduced from the *ECDEU Assessment Manual for Psychopharmacology—Revised*.¹⁵

Therapeutic Effect	Adverse Effects			Outweigh Therapeutic Effect
	None	Do Not Significantly Interfere With Functioning	Significantly Interfere With Patient's Functioning	
Marked—vast improvement; complete or nearly complete remission of all symptoms	01	02	03	04
Moderate—decided improvement; partial remission of symptoms	05	06	07	08
Minimal—slight improvement which doesn't alter status of care of patient	09	10	11	12
Unchanged or worse	13	14	15	16
Not assessed = 00				
Efficacy index: _____				

the patient and parents or legal guardians about any possible adverse effects since the last study visit. These reports, along with investigator observations of any possible adverse effects, were documented at each study visit.

RESULTS

Participant Characteristics

The case series included 6 male and 2 female participants aged 2.75 to 24 years (Table II). Participant 1, who was 2.75 years of age, was considered eligible for the study because he met the diagnostic criteria for ASD and was able to cooperate in an age-appropriate manner with study assessments. The starting dose of L1-79 was 90 mg thrice daily for all participants except participant 5, who began treatment at 22.5 mg 3 times daily. Most dosages were titrated to 200 mg thrice daily, including for the 2.75-year-old child, based on patients' clinical responses and the absence of adverse effects. Participant 8 received a brief course of 400 mg 3 times daily, which was well tolerated; however, no additional benefit was observed. All patients were adherent with their prescribed treatment.

Participant 5 had her benzodiazepine regimen discontinued too rapidly on joining the study, and her withdrawal response necessitated delaying the onset of the experimental treatment. She later resumed L1-79 treatment at 22.5 mg thrice daily, which was titrated up. During L1-79 therapy, her alprazolam dosage was tapered from 1.5 to 1 mg

once daily, then to 0.5 mg as needed, and clonidine treatment was discontinued.

After the washout period and the start of the study, participant 3 was permitted to resume taking an agent previously prescribed for attention-deficit/hyperactivity disorder at a lower dose. Participant 8 restarted use of fluvoxamine extended release at 33% of his original dose for obsessive compulsive disorder. Most patients were stable while taking L1-79 without their legacy medications during the 8-week treatment period (Table III).

Assessments

Total scores on the ABC-C decreased, indicating improvement between the first and last visit for 7 of 8 participants (Figure 1). Improvements differed across participants and appeared somewhat dependent on the severity of the initial impairment. For participants 1, 2, 3, 5, and 7, the scores on all 5 subscales (irritability, lethargy, stereotypy, hyperactivity, and speech) improved, either decreasing and then plateauing or continuously decreasing after initiation of L1-79 treatment. The irritability score of participant 4 improved slightly without changes in any other tested dimension. Participant 6 improved on all subscales except irritability, which worsened after an initial improvement.

Qualitative assessment of ASD core symptoms suggested that 7 of the 8 participants had improvements in communication, relationships,

Table II. Baseline participant characteristics and individual L1-79 dose adjustments during study.

Participant No.	Sex	Age, y	Weight, kg	Comorbidities	Starting Dose	Maintenance Dose
1	M	2.75	15	None	90 mg TID	200 mg TID
2	M	15	115	None	90 mg TID	200 mg TID
3	M	12	33	ADHD	90 mg TID	200 mg TID
4	F	14	50	None	90 mg TID	200 mg TID
5	F	24	50	Anxiety	22.5 mg TID	200 mg TID ^a
6	M	16	61	None	90 mg TID	200 mg TID
7	M	12	48	ADHD	90 mg TID	200 mg TID
8	M	15	46	OCD	90 mg TID	400 mg TID ^b

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive compulsive disorder.

^aThree-step dose escalation.

^bTwo-step dose escalation.

Table III. Autism spectrum disorder medications before and during the study period.

Participant No.	Treatment Regimen Before Study Start	Agents With Discontinued Use Before Study Start	Agents With Continued Use During Study ^a	Changes Made During Study
1	—	—	—	None
2	—	—	—	None
3	Lisdexamfetamine 30 mg once daily	—	—	None
4	Risperidone 1 mg twice daily and mirtazapine 15 mg once daily	Risperidone and mirtazapine	—	None
5	Alprazolam 1.5 mg twice daily ^b and clonidine 0.1 mg as needed	Alprazolam 1.5 mg twice daily ^b	Alprazolam 1 mg twice daily then 0.5 mg as needed	Alprazolam dose reduced to 0.5 mg as needed and use of clonidine discontinued
6	Clonidine 0.2 mg at bedtime, zolpidem 5 mg at bedtime, alprazolam as needed every 6 hours, and risperidone 1 mg once daily	Clonidine, zolpidem, alprazolam, and risperidone	—	None
7	Lisdexamfetamine 20 mg once daily, guanfacine ER 3 mg once daily, dextroamphetamine 7.5 mg once daily, and N-acetylcysteine 600 mg twice daily	Lisdexamfetamine, guanfacine ER, dextroamphetamine, and N-acetylcysteine	—	None
8	Fluvoxamine ER 200 mg once daily, quetiapine 100 mg 4 times daily	Fluvoxamine and quetiapine	—	Restarted treatment with fluvoxamine ER 100 mg once daily

Abbreviation: ER, extended release.

^aThe protocol called for a 2-week washout of psychotropic medications, but some individuals were permitted to continue their regimens based on participant-specific factors.

^bDiscontinued use after initial intake but before second intake.

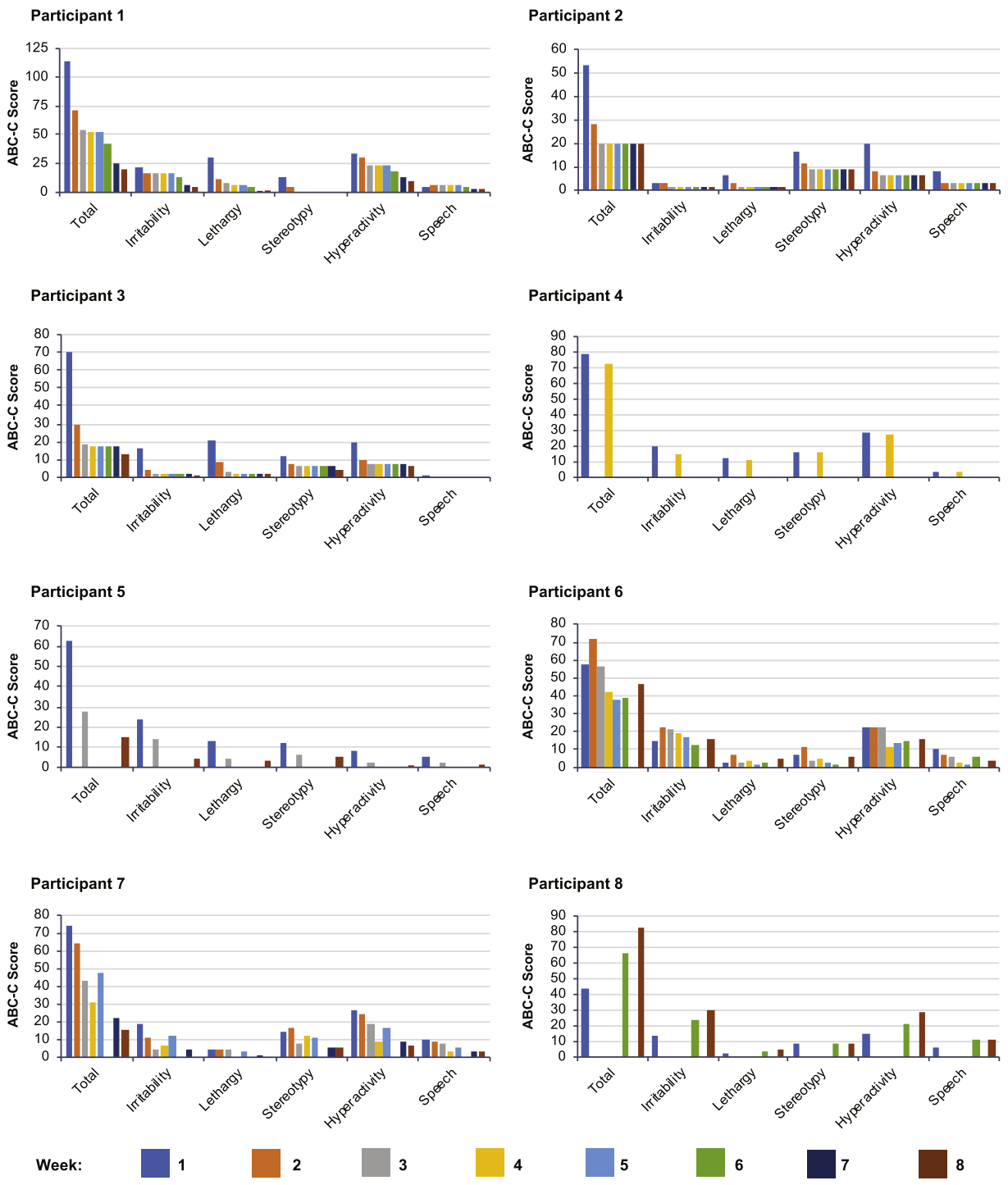


Figure 1. Aberrant Behavior Checklist–Community (ABC-C) scores. Domain scores for each participant during weeks 1 to 8. Because of participant-specific factors, ABC-C scores were not recorded at all visits for all participants.

behavior, and social functioning, whereas participant 8 had improvement in communication and relationships but little or no change in behavior or socialization. Parents and other participant contacts, such as teachers and school bus drivers, anecdotally reported increased socialization, affection, and behavioral improvements.

Parent reports as measured by the CPRS at 4-week intervals stated continuing improvements for 6 of 8 participants during 8 weeks of treatment (Figure 2).

ADOS scores were determined at screening and week 10 and improved by 31% to 47% for 4 of the 6 participants tested, including participant 8, who had worsening on most other scales (Figure 3). The ADOS score of participant 6 worsened, and the score of participant 7 remained the same. The ADOS score decreased from 9 to 6 for participant 1 and 21 to 13 for participant 2. Participant 3 experienced a decrease from 12.5 to 8 and no longer met the criteria for a diagnosis of ASD.

As shown in Figure 4, CGI assessment showed decreased ASD severity after 8 weeks of L1-79 treatment in 7 participants. For participants 1, 2, 3, 5, 6, and 7, the CGI efficacy index was 05, indicating modest improvement with at least partial resolution of symptoms. Participants 4 and 8 had a score of 09, indicating minimal improvement and no change in status or care needs.

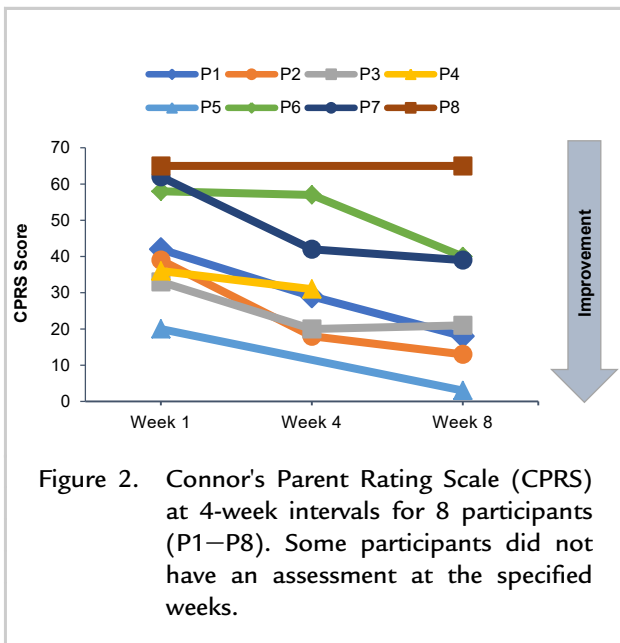


Figure 2. Connor's Parent Rating Scale (CPRS) at 4-week intervals for 8 participants (P1–P8). Some participants did not have an assessment at the specified weeks.

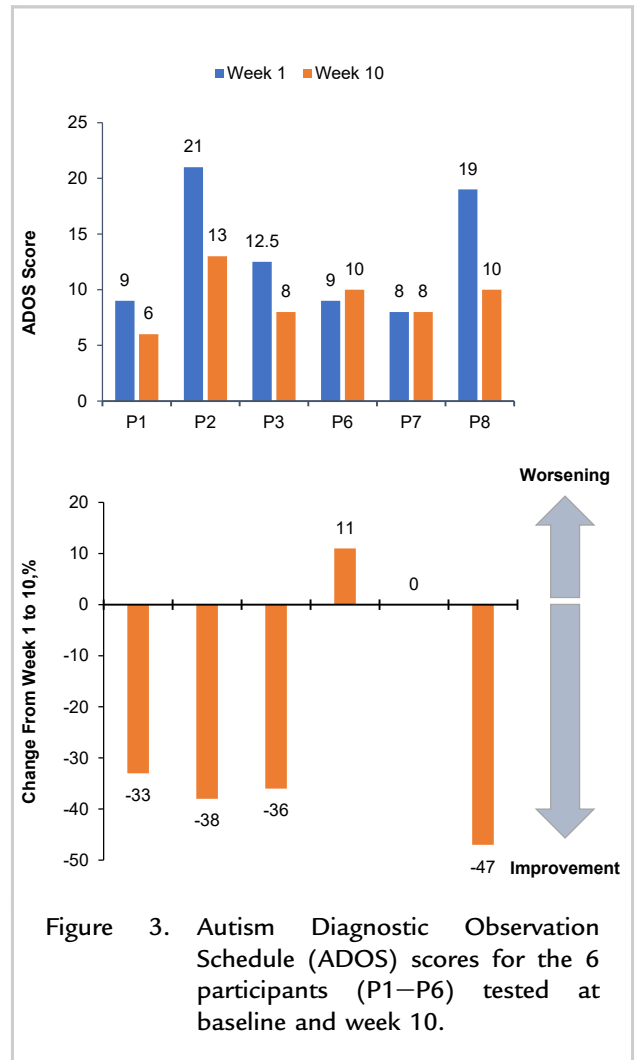


Figure 3. Autism Diagnostic Observation Schedule (ADOS) scores for the 6 participants (P1–P6) tested at baseline and week 10.

Adverse Events

Three adverse events were reported. Two participants went to sleep early on the first night of treatment only (coded as fatigue), and 1 reported hyperhidrosis during the study. All adverse events were mild and resolved spontaneously without intervention.

DISCUSSION

The proposed mechanism of action of L1-79 for the treatment of ASD is consistent with the assumption that an imbalance exists between catecholaminergic systems and the modulators of aminergic systems in the CNS and periphery.¹⁷ Excess levels of nerve growth factor (NGF) and brain-derived NGF (BNGF), which are released into the catecholamine synaptic cleft, can cause branching and arborization

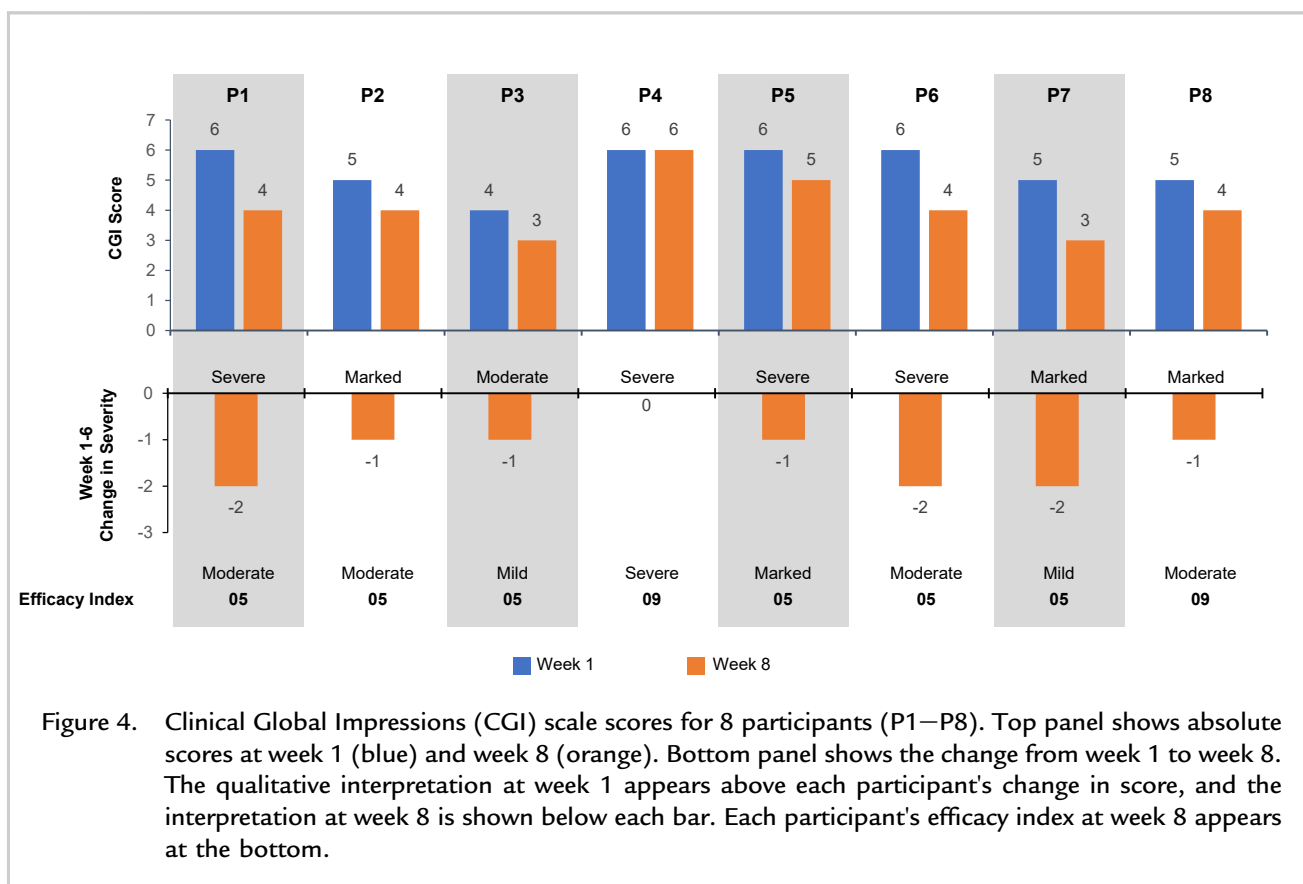


Figure 4. Clinical Global Impressions (CGI) scale scores for 8 participants (P1–P8). Top panel shows absolute scores at week 1 (blue) and week 8 (orange). Bottom panel shows the change from week 1 to week 8. The qualitative interpretation at week 1 appears above each participant's change in score, and the interpretation at week 8 is shown below each bar. Each participant's efficacy index at week 8 appears at the bottom.

of synaptic terminals, thus increasing the strength of catecholaminergic neurotransmission.^{18,19} Because growth factors are an obligate component in these synapses, elevated levels of NGF and BDNF become chronic, along with elevated levels of dopamine and other catecholamines from these hypertrophic nerve terminals. The result may be a hypertrophy of the synaptic architecture, resulting in a persistent imbalance between aminergic systems and their offsets, which can lead to overstimulation of some CNS tracts and depletion of others. Consequently, increased dopamine activity within the CNS and the gut is associated with ASD, repetitive stereotyped behaviors, and defiant and anxiety disorders.^{17–19}

By reducing presynaptic catecholamine synthesis, storage, and release, L1-79 may reduce the associated release of NGF and BDNF, rebalancing catecholaminergic mechanisms in the brain, gut, mesentery, and elsewhere. These effects are not mimicked by receptor-blocking agents that reduce postsynaptic depolarization without addressing the underlying hypertrophic dendritic architecture.^{17–19}

If this proposed mechanism of action of L1-79 in ASD is correct, reduced catecholamine synthesis, storage, and release should improve ASD symptoms. In the long term, reducing catecholamine release may enable the hypertrophic sympathetic nervous system to regress to a homeostatic configuration. The initial response observed in most of the present case series participants, along with the stability of patients whose legacy medication regimens were stopped or dosages reduced, suggests that L1-79 may be effective in ASD.

ASD is frequently diagnosed in children as young as 2 years and has a lifelong effect on patients. Despite decades of research, ASD treatment remains an unmet need for patients of all ages. On an anecdotal basis, parents and others well known to participants frequently reported increased affection from study participants, and behavioral improvements were anecdotally noted by teachers, school bus drivers, and others. On the basis of follow-up observations by the investigators, these effects appeared to persist after the study was completed and treatment terminated. We

hypothesize that increased duration of treatment may result in better retention of treatment effects because of reduced growth factor release and resulting regression and diminution of sympathetic synaptic tone as well as restored balance between the sympathetic and parasympathetic nervous systems. These hypotheses deserve further study.

Agitation and irritability are hallmarks of ASD, albeit not core symptoms. Risperidone received approval for use in ASD based exclusively on its ability to reduce autism-associated irritability. However, risperidone and aripiprazole, the only medications approved for ASD in the United States, treat only irritability, not the core symptoms of ASD, and they have very unfavorable safety profiles.⁴ Because of a lack of appropriate therapy, medical management of ASD may include off-label use of other antidepressant, antianxiety, antipsychotic, anti-attention-deficit/hyperactivity disorder, or other psychotropic medications, which frequently carry a heavy adverse effect burden.^{20,21} Obesity, metabolic syndrome, and cardiovascular adverse effects are common comorbidities associated with these agents that increase patients' long-term health risks.^{4,22} With L1-79, we observed reductions in autism-associated irritability and anxiety as well as improvements in the core symptoms of ASD measured with the ADOS and ABC-C scales. The judgment of the investigators that these changes were clinically meaningful is documented in the CGI scores. These clinical observations were supported by qualitative assessments by investigators, caregivers, teachers, and other individuals who interacted with study participants.

In this case series, L1-79 was well tolerated and had clinical utility to address the core symptoms of ASD. Typically, ADOS scores remain fairly stable during the lifetime of patients with ASD,²³ yet in this study, the ADOS scores improved meaningfully in 6 of 8 participants tested after 8 weeks of treatment, indicating a reduction of disease severity. Along with observed improvements in other scales, this result suggests that L1-79 may affect the ASD disease process through inhibition of catecholamine synthesis, although the relationship between the proposed mechanism of action of L1-79 and its clinical effects requires further study.

The small number of participants with a wide age distribution, the lack of blinding, and the lack of statistical analysis prevent us from drawing conclusions about the efficacy of L1-79. The

assessment scales presented other limitations. The ABC-C assessment only allowed for notations of worse, no change, or improved and thus failed to reveal the full magnitude of ongoing improvements. The unprecedented changes in participants' ADOS scores further suggest a need for ASD metrics that can better measure changes in core symptoms because the ADOS is not typically used as an outcome measure.

Despite these limitations, the findings presented in this first look at L1-79 as a treatment for ASD support further study of L1-79 as a potential treatment for the core symptoms of ASD. A subsequent Phase II randomized, blinded, placebo-controlled trial of L1-79 as a potential treatment for the core symptoms of ASD is complete and currently being analyzed to further assess its effects in patients with ASD (NCT02947048). The US Food and Drug Administration has given this program fast-track status and, based on the data from the first 2 trials, has approved L1-79 for pivotal trials.

CONCLUSIONS

L1-79 was well tolerated and had clinical utility to address the core symptoms of ASD. Contrary to usual clinical experience, ADOS scores improved meaningfully in 6 of 8 participants tested after 8 weeks of treatment, indicating a reduction of disease severity. Along with other observed improvements in the core symptoms of ASD, this result supports the hypothesis that the presynaptic inhibition of catecholamine synthesis by L1-79 may have clinical utility in ASD; however, this will require further study.

DISCLOSURES

J.R. is an employee of Yamo Pharmaceuticals. E.J.B. and F.P.H. have no financial interests to declare.

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