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RESEARCH ARTICLE

Ecopipam as a pharmacologic treatment of stuttering

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BACKGROUND: Stuttering, also known as childhood-onset fluency disorder, is a chronic neurodevelopmental disorder that affects 1% of the population and can greatly impact an individual's social, occupational, and academic functioning. Prior research has shown dopamine D2 antagonists are effective in reducing the severity of stuttering symptoms, but these compounds can be associated with metabolic and movement disorder adverse effects. Ecopipam is an investigational medication that acts as a selective dopamine D1 receptor antagonist. This mechanism should reduce the likelihood of metabolic and movement disorder adverse effects of D2 antagonists.

METHOD: This open-label pilot study investigated ecopipam in the treatment of adults who stutter.

RESULTS: The results showed that a majority of participants demonstrated improvement in their stuttering. The medication was well tolerated.

CONCLUSIONS: These positive, preliminary findings suggest that a double-blind, randomized controlled clinical trial to examine the efficacy of ecopipam in the treatment of stuttering is warranted.

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TABLE 1
The mean and standard deviation comparisons between baseline and end of study for each of the 7 measures

Measure	Baseline[a]	End of study[a]	Cohen's *d*
OASES score	3.07 (0.31)	2.47 (0.31)	+1.918
SSS score	94.4 (28.6)	57.4 (25.9)	+1.358
SSI-4 score	35.4 (9.8)	26.4 (12.9)	+0.785
SSI-4 duration, seconds	10.4 (11.9)	4.3 (5.1)	+0.671
Reading rate, syllables per minute	106.6 (65)	137.6 (77)	–0.433
%SS-speaking SSI-4	12.5 (9.2)	8.9 (9.8)	+0.379
%SS-reading SSI-4	17.7 (11.7)	13.7 (9.8)	+0.370

[a]Mean (standard deviation)

%SS: percent syllables stuttered; OASES: Overall Assessment of the Speaker's Experience of Stuttering; SSI-4: Stuttering Severity Instrument–Fourth Edition; SSS: Subjective Screening of Stuttering.

INTRODUCTION

Stuttering is a chronic neurodevelopmental disorder that affects 1% of the population. Stuttering usually begins in childhood and often persists throughout the lifetime. Natural recovery can occur in children; however, if stuttering persists beyond age 8, the symptoms often continue throughout the lifetime.[1] Stuttering, also known as childhood-onset fluency disorder, can greatly impact an individual's quality of life. Unfortunately, current forms of speech therapy are associated with high rates of relapse and low response rates.[2]

Much has been learned in recent years about the neurophysiology of stuttering. Findings of differences in neurologic structure and function support the need for further studies of the efficacy of pharmacologic treatment.[3,4] Stuttering has been found to be amenable to pharmacologic treatment.[5-12] Manipulating dopamine appears to be a viable target for stuttering pharmacotherapy because dopamine may play a central role in the etiology of stuttering.[13,14] Previous studies suggest that stuttering may be associated with elevated cerebral dopamine levels; this presumably is the reason that dopamine antagonist medications have efficacy in improving stuttering symptoms.[8,15] Unfortunately, many dopamine antagonist medications are associated with adverse events such as movement disorders and metabolic abnormalities.

Ecopipam is an investigational medication that acts as a selective dopamine D1 receptor antagonist. It has little affinity for dopamine D2 receptors and no reports of parkinsonian-like extrapyramidal symptoms or metabolic concerns typically seen with D2 antagonists.

The primary purpose of this pilot study was to investigate, in a preliminary manner, the efficacy of ecopipam in adults who present with moderate to very severe developmental stuttering. The hypothesis was that ecopipam effectively reduces stuttering symptoms as measured on the Stuttering Severity Instrument-Fourth Edition (SSI-4), Clinical Global Impression–Severity (CGI–S) scale, Clinical Global Impression–Improvement (CGI–I) scale, Subjective Screening of Stuttering (SSS),[16] and the Overall Assessment of the Speaker's Experience of Stuttering (OASES).[17] The secondary purpose of this study was to determine tolerability of this compound in individuals who stutter.

METHODS

Participants

Ten male and female volunteers (age 18 to 65), were recruited from our interested subject database accumulated at the University of California Riverside School of Medicine. They were selected based on the following criteria: (1) reported that the onset of stuttering was prior to age 10; (2) rated to be at "moderate severity" or greater on the SSI-4; (3) rated to be at a ≤12 on the Montgomery-Åsberg Depression Rating Scale (MADRS); and (4) English-speaking.

The following exclusion criteria were used: unable to voluntarily consent, the presence of a known neurologic basis for the stutter (eg, from Parkinson's disease or traumatic brain injury) or the presence of an unstable medical or psychiatric illness, active substance abuse within 3

TABLE 2
Severity ranking changes from baseline on the SSI-4

Participant	Baseline	End of study
001	26 (moderate)	13 (very mild)
005	46 (very severe)	42 (very severe)
007	31 (moderate)	22 (mild)
008	27 (moderate)	17 (very mild)
010	46 (very severe)	38 (very severe)

SSI-4: Stuttering Severity Instrument–Fourth Edition.

months, or any illness that would require the concomitant use of a CNS-active medication.

This was a single-center, open-label study in which the participants provided written informed consent. Potential participants underwent a thorough clinical screening with physical examination, vital signs, and laboratory testing. One male participant (009) withdrew consent. Two participants withdrew: one, a male (004), reported an inability to commute to the center; the other, a female (006), preferred a previous medication. Two participants who qualified for the study were identical twin males, and the results were not included in the final analysis. Therefore, final data analysis included 5 participants.

Design

This study was an open-label treatment efficacy design, comparing baseline to the completion of 8 weeks of administration of ecopipam. Participants were rated at baseline and at the end of 8 weeks on the primary endpoints, the SSI-4, SSS, and OASES. Tolerability was assessed by physical and neurologic examination, laboratory examination, and standardized assessments, including the Columbia-Suicide Severity Rating Scale (C-SSRS), MADRS, Simpson-Angus Scale (SAS), Barnes Akathisia Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS). To obtain the SSI-4, participants were video/audio recorded.

All participants began at 50 mg/d of ecopipam for 2 weeks, and if this dosage was tolerated, were increased to 100 mg/d for the remainder of the 6 weeks.

Data analysis

The second author (LL) scored all SSI-4, OASES, and SSS. The participants produced a median of 1,200 to 1,400 spontaneous syllables per SSI-4 Speaking Task (range: 900 to 2,300). There was no difference (W = −2; $P > .05$) in syllables counted in the baseline (median = 1,200; range = 1,000 to 2,100 syl) and end of study (median = 1,400; range = 900 to 2,300 syl). For the SSI-4 reading task, the participants produced approximately 201 syllables in the Cesar Chavez reading and 186 syllables in the Harriet Tubman reading, both 7th grade reading passages, presented in counterbalanced order to baseline and end-of-study data points. The second author coded each whole-word repetition, sound-syllable repetition, and audible or inaudible sound prolongation (block) as a "stutter," or stutter-like disfluency, to determine percent syllables stuttered (%SS) as per the SSI-4 manual. She also coded all other types of disfluencies. Questionable stutters were indicated as such, and not counted in final data.

Reliability and validity

There was an unsuccessful attempt to blind the second author to whether the sample was drawn from the baseline or end-of-study data point due to: (a) the need to determine if the participant was moderate or higher on the SSI-4 in order to know whether to continue with the study (the initial SSI-4 data served as data), and (b) the time references that were occasionally made during the recordings. To address this, all recordings will be uploaded to FluencyBank for any interested investigators to score independently. Inter- and intra-judge reliability for the SSI-4 were performed by the second author in several steps: (1) performed random selection of 20% of the data across the 5 participants; (2) requested a trained graduate assistant who would later serve in inter-judge reliability capacity to randomly re-label the data as baseline/end of study; and (3) re-scored the selected data for intra-judge reliability 6 to 8 weeks after the second author performed first scoring. Cohen's kappa was used to account for possible chance agreement. For intra-judge reliability for the SSI-4 reading task %SS: kappa = 0.97 to 1.0; for %SS for the speaking task: kappa = 0.88 to 0.89. For inter-judge reliability: SSI-4 reading task (%SS): kappa = 0.93 to 0.94; for speaking task (%SS): kappa = 0.97 to 1.0.

Statistical analyses

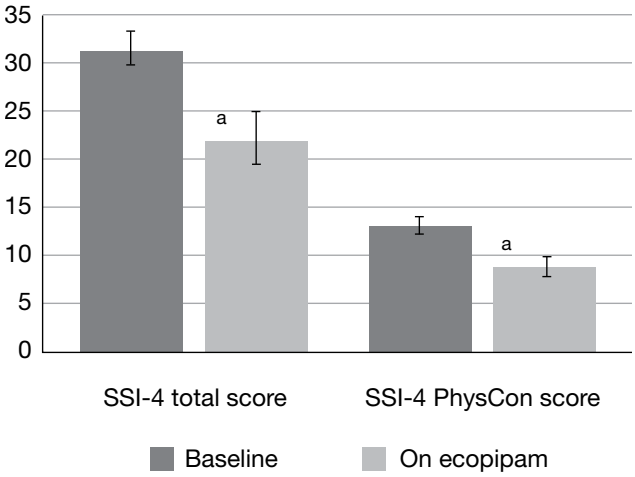
In order to measure the clinical efficacy of this medication intervention, effect sizes (Cohen's *d*) were computed as the differences in matched pair means divided by the "pooled standard deviation," as recommended by Rosnow and Rosenthal.[18] The nonparametric Wilcoxon signed-rank

test was used because it was not possible to assume a normality with only 5 participants. Percent overlapping data was not computed, but medians and standard error bars are displayed graphically.

RESULTS

TABLE 1 shows the mean and standard deviation comparisons between baseline and end of study for each of 7 measures of interest in order of size of the Cohen's *d* effect sizes. **TABLE 2** shows the severity ranking changes from baseline on the SSI-4.[19] In terms of observed stuttering behaviors, the **FIGURE** shows the significant (n = 5; $W = +15$; $P < .05$) differences found between the baseline and end-of-study conditions in %SS. Efficacy was also shown on the participant-rated SSS, and ecopipam was associated with improved quality of life as measured on the OASES. Ecopipam was well tolerated: all participants tolerated the 100 mg/d dosage. No reported adverse events were observed, with no signals for increased depression as noted on the MADRS or suicidal thoughts as noted on the C-SSRS. Furthermore, there were no adverse events noted on the SAS, BARS, or AIMS.

FIGURE
Percent syllables stuttered (%SS) in SSI-4 reading and speaking



[a]$P < .05$

PhysCon: physical concomitant; SSI-4: Stuttering Severity Instrument–Fourth Edition.

DISCUSSION

This preliminary study investigated the efficacy and tolerability of ecopipam for adults who present with moderate to severe stuttering. This was an open-label, pilot design to preliminarily investigate the use of ecopipam in stuttering. Ecopipam was well tolerated without adverse events. Participants with moderate stuttering made significant gains in overall stuttering severity as rated by the SSI-4; the 2 participants with very severe stuttering showed minimal gains in overall severity.

CONCLUSIONS

In summary: (1) fluency improved, with reduced percent syllables stuttered in both reading and spontaneous speaking; (2) reading completion was faster; (3) stutter duration of the 3 longest stutters improved; and (4) scores on the OASES improved. This preliminary study showing improvement in stuttering severity across multiple measures supports the need for a double-blind, randomized controlled clinical trial to examine the efficacy of ecopipam in the treatment of stuttering. ■

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