DYSTONIA

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Efficacy and safety of valbenazine in the treatment of cervical dystonia: a pilot study

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Background: Vesicular monoamine transporter-2 inhibitors have provided on-label success in the treatment of tardive dyskinesia (TD) and Huntington's disease chorea (HDC). A similar pathophysiological pathway for cervical dystonia suggests valbenazine (VBZ) could be beneficial in this condition.

Objective: To determine the efficacy of VBZ in reducing symptoms of pain and posturing and improving quality of life in subjects with cervical dystonia.

Methods: This was an open-label, prospective study of subjects with a clinical diagnosis of cervical dystonia currently being treated with botulinum neurotoxin (BoNT) for >6 months. Valbenazine was titrated to 80 mg per day with no change in BoNT dosage or muscle location. Evaluations were performed 4 weeks prior to the subject's scheduled BoNT treatment date BoNTmax/-VBZ (time 1) compared to 4 weeks prior to the subject's next BoNT treatment date BoNTmax/+VBZ (time 4). TheBoNT injection treatment date BoNTmin/VBZ dispensing (time 2) and the next BoNT injection treatment date BoNTmin/+VBZ (time 5) were compared. Efficacy was assessed using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTR), Neck Pain Disability Index (NPDI). Visual analog scale (VAS, 0–10) for pain/pulling/jerking, Pittsburgh Sleep Quality Index (PSQI), Clinical Global Impression of Change (CGIC) and Patient Global Impression of Change (PGIC) Scales.

Results: Fourteen subjects were enrolled and followed for a total of 16 weeks. TWSTRS Total Score was significantly improved at time 4 compared to time 1 ($p = 0.02$), as well as VAS 0–10 scores for 24 Hour ($p = 0.001$), Past Week Pull ($p = 0.0001$), and Past Week Jerk ($p = 0.04$). TWSTRS Total Score was significantly improved at time 5 compared to time 2 ($p = 0.02$) as well as 24 Hour Pull ($p = 0.01$), 24 Hour Jerk ($p = 0.04$), Past Week Pull ($p = 0.002$), and Past Week Jerk ($p = 0.02$). Subjective improvement was reported at times 3, 4 and 5 on CGIC and PGIC Scales. No significant improvements were seen in the PSQI and NPDI. The medication was tolerated well with fatigue as the most common adverse effect.

Conclusion: This exploratory study demonstrates a potential benefit in the addition of VBZ for the treatment of cervical dystonia associated with severe pain and posturing.

KEYWORDS

cervical dystonia, valbenazine, dystonia, botulinum neurotoxin, clinical research

Introduction

Cervical dystonia (CD) is a disabling chronic condition that affects 8 individuals per 100,000 [1, 2]. Like other forms of focal dystonia, cervical dystonia's pathophysiology is rooted in the unbalanced contraction of an agonist muscle with impaired contraction of an antagonist muscle [3]. This impaired reciprocal inhibition causes symptoms of abnormal posturing, pulling, and twisting of the neck muscles which can be associated with pain [1, 3]. The pain associated with cervical dystonia is not entirely understood. The degree of contraction and patient reported pain have been found to be correlated; but not always consistently associated with pain [4]. This has led to the belief that specific pain pathways play a role in the pain experienced by those with cervical dystonia [2].

First-line treatment for cervical dystonia has included injections of botulinum neurotoxin (BoNT) every 12–16 weeks since the 1980s [5]. Chemodenervation treatment with BoNT may target muscles including the splenius capitis, scalenes, and levator scapulae on the ipsilateral side, and the sternocleidomastoid on the contralateral side [3]. Although BoNT has been found to successfully reduce muscle contractions, between 30%–46% of patients report inefficiency, and subsequently discontinue BoNT treatments. The suspected reasons patients discontinue treatment include: the formation of neutralizing antibodies to BoNT, improper dosing, improper injection methods, and subjective feelings of inefficacy [1]. Other patients may experience suboptimal effect with little oral pharmacologic options for treatment. There is a significant need for an increased variety of treatment modalities to address the pain and disability experienced by patients with cervical dystonia.

Although cervical dystonia is considered an idiopathic condition, there are several working theories being studied in the effort to better target dystonic contractions. Lower thalamic levels of the inhibitory neurochemical gamma-aminobutyric acid (GABA) have been demonstrated using magnetic resonance spectroscopy in patients with cervical dystonia [6]. Decreased GABA binding has also been shown in the sensorimotor cortex, motor cortex, insula, and anterior cingulate in patients with focal dystonia's using C-flumazenil PET/CT scanning [6]. Abnormalities in dopamine neurotransmission may also play a large role in the pathophysiology of cervical dystonia [7]. Dystonia is seen in hyperkinetic movement disorders that affect dopamine neurotransmission such as Huntington's Disease (HD), tardive dyskinesia (TD), and motor tics where dopaminergic pathways are also known to be dysregulated. Treatment of these conditions has relied on reducing quantities of dopamine available in the synaptic cleft for neurotransmission [8, 9].

The only FDA approved medication class for the treatment of TD and HD chorea is vesicular monoamine transporter 2 inhibitors (VMAT2 inhibitors). Valbenazine (VBZ) is one of the three VMAT2 inhibitors (other two are deutetrabenazine and tetrabenazine) currently available in the United States. Valbenazine and other VMAT2 inhibitors act to reduce dopamine and monoamine packaging within presynaptic vesicles, which subsequently reduces dopamine levels within the synaptic cleft [10]. Although the pharmacodynamic profile of VBZs similar to tetrabenazine and deutetrabenazine, when metabolized VBZ is converted into only one active stereoisomer, (+)- alpha-dihydrotetrabenazine (R,R,R-HTBZ), which has the strongest affinity for VMAT2 [9, 10]. Having only one active stereoisomer allows for VBZ to be considered the most selective of the three VMAT2 inhibitors [8, 10]. Additionally, valbenazine was first FDA approved in 2017 as a VMAT2 inhibitor with a 20 h half-life, this extended half-life allows for once daily dosing.[9,10]

Valbenazine has successfully treated the symptoms of tardive dyskinesia where the leading theory on pathophysiology involves dopamine D2 receptor expression upregulation following prolonged blockage by antipsychotic medications [8]. Valbenazine has also successfully treated chorea associated with HD, where the pathophysiology includes increased dopamine neurotransmission [9].

Valbenazine's prior on-label success in the treatment of several dopamine-mediated movement disorders provides promise for other hyperkinetic disorders that have a paucity of treatment options [8, 9]. This exploratory study tested the hypothesis that VBZ treatment would decrease pain, spasms, and pulling, and improve quality of life and sleep quality in subjects with moderate to severe cervical dystonia already receiving BoNT treatment.

Materials and methods

Participants

This was an open-label, prospective single center study conducted at the research office of a by a board-certified

neurologist, with expertise in treating CD with BoNT, from October 2021 until October 2022. Individuals aged 18–85 years old with a clinical diagnosis of idiopathic cervical dystonia for at least 6 months with at least 3 months of stable botulinum toxin dosage therapy were eligible. The participants were also required to have moderate to severe head tremor and/or dystonic posturing determined by the clinician. Exclusions included a diagnosis of tardive dyskinesia or any known exposure to neuroleptics, previous surgical intervention for CD, exposure to neuroleptic medication, and any significant muscular disease (such as myasthenia gravis) or other structural abnormalities such as cervical contractures that could interfere with the results of the trial. Other exclusions included predominant anterocollis, concomitant use of a strong CYP3A4 inhibitor, moderate to severe hepatic impairment, and previous exposure or hypersensitivity to VBZ.

All research procedures were conducted in accordance with the ethical procedures outlined in the Declaration of Helsinki and registered at *ClinicalTrials.gov ID: NCT05157100*. The study was approved by the WCG Institutional Review Board, and all participants provided written informed consent prior to taking part in any study procedures.

Study design

Subjects were seen every 4 weeks for a total of 5 visits with an initial 4 weeks of baseline evaluation and a 12-week treatment period. Standard assessments including unstructured patient reporting of adverse events since the prior visit were collected at every visit. Table 1 provides complete details on study assessments and timing for each visit. Visit 1 was the screening/baseline study, with subjects beginning VBZ 40 mg and receiving their BoNT injection at visit 2. Valbenazine was titrated to limit side effects from 40 mg to 80 mg at visit 3 based on tolerability. The dosage was maintained or decreased to 40 mg per patient preference if significant side effects occurred on the higher dose. Botulinum toxin injections were also given at visit 5 and the subjects exited the trial.

The standard of care for BoNT therapy is typically administration every 12 weeks. Thus, participants were given their BoNT injection at visit 2, 12 weeks after their prior injection, and visit 5, 12 weeks after visit 2. At visit 3, subjects theoretically would be experiencing the maximum effects of their botulinum toxin injection (BoNTmax). At visit 1 and visit 4, participants would be at the 8-week mark of their botulinum toxin effects, and at visit 2 and visit 5 they would be at the 12-week mark (BoNTmin). Therefore, in the analysis, visits 1 and 4 (BoNTmax) and visits 2 and 5 (BoNTmin) were compared as the botulinum toxin effects would be at a similar point in the treatment cycle. Figure 1 outlines the study timeline with visit and dosing schedule.

Outcome measures

The primary objective of the study was to determine the efficacy of VBZ in improving the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) scores. The TWSTRS total (scored 0–85), composed of the Severity (0–35), Disability (0–35), and Pain (0–20) subscales, is a validated, disease-specific scale in which higher scores indicate greater impairment [11].

Secondary objectives included changes in 24-h and past week pain, jerking, pulling measured by the visual analog scale (VAS, 0–10), changes in Neck Pain Disability Index (NPDI) [12], changes in sleep quality measured by the Pittsburgh Sleep Quality Index (PSQI) [13], and treatment efficacy measured by both investigator assessment of efficacy using the Clinical Global Impression of change (CGIC) and patient assessment of efficacy using the Patient Global Impression of Change (PGIC).

The TWSTRS, VAS, and NPDI were performed at every visit, the PSQI was performed at visits 2–5, and the CGI and PGIC were performed at visits 3–5. Therefore, when comparing visit 1 (BoNTmax/-VBZ) and visit 4 (BoNTmax/+VBZ) the TWSTRS, VAS, and NPDI were compared between visit 1 (BoNTmax/-VBZ) and visit 4 (BoNTmax/+VBZ).When comparing visit 2 (BoNTmin/VBZ dispensing) and visit 5 (BoNTmin/+VBZ), the TWSTRS, VAS, NPDI, and PSQI were compared between visit 2 (BoNTmin/VBZ dispensing) and visit 5 (BoNTmin/+VBZ).

The CGIC and PGIC scales were ratings done by the clinician and patient that showed perceived improvement. The CGIC scale measured The CGIC is a −3 to +3 point scale and the PGIC in a −4 to +4 point scale, with zero representing no improvement. The PGIC scale was also divided into 3 sections, reporting potential change in pulling/spasm, pain, and tremor/jerking. The CGIC scale asked the clinician to compare the subject at their condition on admission into the study, while the PGIC scale asked the patient to compare themselves to the last 4 weeks. These scales were performed at visit 3–-5.

Statistical analysis

SAS v 9.4 was used to perform all statistical analysis with a predefined significance level of 0.05. The data was normally distributed, and parametric tests were used for the analysis. ANOVA was used to find out the relationship between Visits 1, 2, 3, 4, and 5 and scoring for each of the scales. T-test was used to analyze the relationship between visit 1 and visit 4, visits 2 and visits 5. T-test were also used to compare the mean scores for different doses of VBZ. The Frequency Procedure is used to

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TABLE 1 Visit schedule with procedures.

Procedure	Visit 1/Baseline	Visit 2	Visit 3	Visit 4	Visit 5/Exit
Informed consent	X				
Inclusion/exclusion	X				
Demography	X				
Medical history	X				
Medication history	X				
Physical exam	X				
Vital signs	X	X	X	X	X
TWSTRS	X	X	X	X	X
24 hour/past week VAS for pain, pulling, spasms, jerking	X	X	X	X	X
Neck pain disability index	X	X	X	X	X
Urine pregnancy test	X				
12 lead ECG	X				
Clinical global impression of change			X	X	X
Patient global impression of change			X	X	X
Pittsburg sleep quality index			X	X	X
Investigational product (IP) dispensing		X			
IP accountability/collection			X	X	X
AE/SAE recording					
Concomitant medications	X	X	X	X	X
C-SSRS	X				
Blood draw/lab prep	X				

analyze the distribution of the Current Ingrezza Dose (mg) and the occurrence of Adverse Events. Contingency tables and Chi-Square tests were used to examine the relationship between the dose and adverse events. Fisher's Exact Test was used to validate the results due to the small sample size.

Results

A total of 20 subjects were enrolled. Out of the 20, there were 6 early-terminations. One of the participants exited due to patient request after the first visit due to severe neck and shoulder pain after screening and before taking the study drug. One of the participants was not included in the analysis as they no showed for visit 5. Four participants exited due to side effects. Therefore, a total of 14 patients (70%) completed the study including 6 males (43%) and 8 females (57%). Table 2 reviews the distribution of subjects ages, age of dystonia diagnosis, and duration of diagnosis.

Dosing

All subjects started on 40 mg of VBZ at visit 2 with recommended increase to 80 mg at visit 3 based on tolerance and subject preference. Ten of the fourteen subjects elected to increase to 80 mg at visit 4 but two of the ten elected to decrease to 40 mg because of adverse effects. Therefore, at visit 4 four subjects were taking 40 mg and ten were taking 80 mg and at visit 5 six subjects were taking 40 mg and eight were taking 80 mg.

Visit 1 and visit 4 comparison

These visits are 4 weeks aways from botulinum toxin injections. The main variable between visit 1 and 4 is the addition of VBZ. Significant decreases were found at visit 4 compared to visit 1 for TWSTRS Total ($p = 0.02$), VAS 24-h Pull with a large effect size ($p = 0.001$), VAS Past Week Pull ($p = 0.0001$), and VAS Past Week Jerk with a small effect size

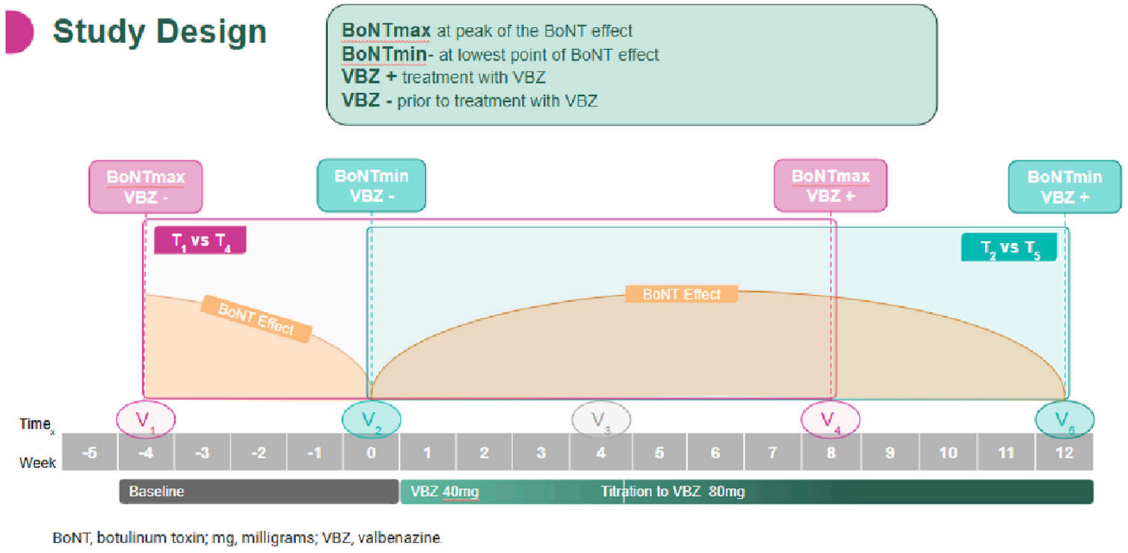

FIGURE 1
Study timeline with visit and dosing schedule.

TABLE 2 Subject characteristics.

	Male	Female	
Number of subjects	6 (43%)	8 (57%)	
	Mean	**Minimum**	**Maximum**
Age (years old)	63	44	84
Age of onset of *CD* (years old)	55	39	76
Duration of *CD* diagnosis (years)	9	3	32

(p = 0.04) (Figure 2). No significant changes were seen in the NPDI, VAS 24-h Pain, VAS 24-h Jerk, VAS Past Week Pain, TWSTRS Severity Subscale, TWSTRS Pain Subscale, and TWSTRS Disability subscale.

Visit 2 and visit 5 comparison

These visits represent the end of the last cycle of botulinum toxin and commencing of the next cycle. The main variable between Visit 2 and 5 is the addition VBZ. Significant decreases were found for VAS scores for 24 Hour Pull (p = 0.01), 24 Hour Jerk (p = 0.04), Past Week Pull (p = 0.002), VAS Past week Jerk (p = 0.02), TWSTRS Pain (p = 0.05), TWSTRS Disability (p = 0.03), and TWSTRS Total (p = 0.02) (Figure 3). No significant decreases were found for VAS 24 Hour Pain, VAS Past Week Pain, and TWSTR Severity.

Other scales

Results for clinical global improvement of change (CGIC) and patient global improvement (PGIC) scales

Figures 4, 5 reveal the values that were reported at visits 3–5. These visits were each compared to a baseline of no improvement and were compared between each visit. Both the CGIC scale and PGIC scale were found to be statistically significant ($P < 0.05$) when each visit was compared to a baseline of zero. They were not found to be statistically significant when compared between each visit.

Sleep quality throughout the study was measured by the Pittsburgh Sleep Quality Index (PSQI) with ratings for all participants averaging above 6 for all visits. Sleep ratings were variable throughout the study with no corollary trend between sleep quality and VBZ treatment dosing.

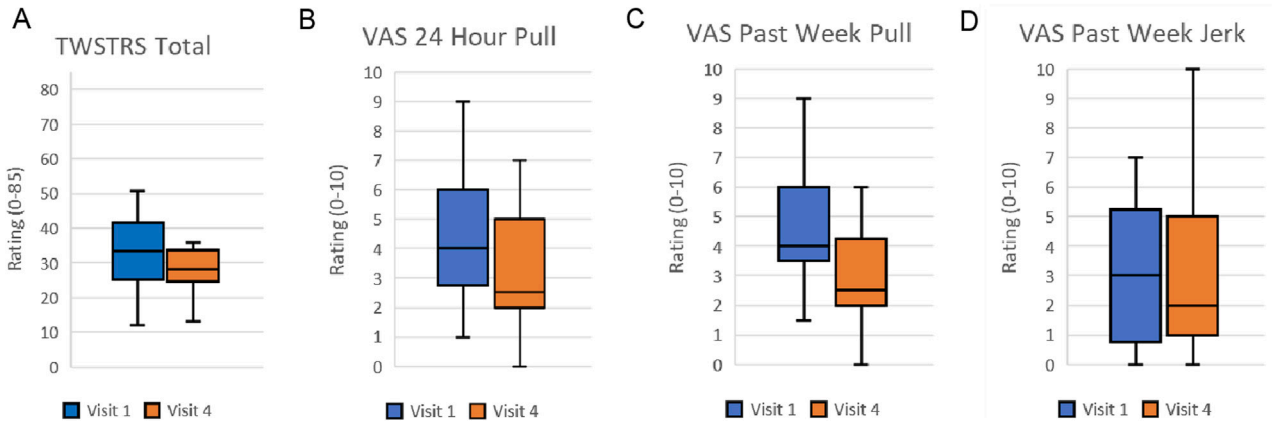

FIGURE 2
(BoNTmax/-VBZ) and visit 4 (BoNTmax/+VBZ) comparison. **(A)** Twstrs total score (p = 0.02) and VAS 0–10 scores for **(B)** 24-h Pull (p = 0.001), **(C)** past week Pull (p = 0.0001), and **(D)** past week Jerk (p = 0.04).

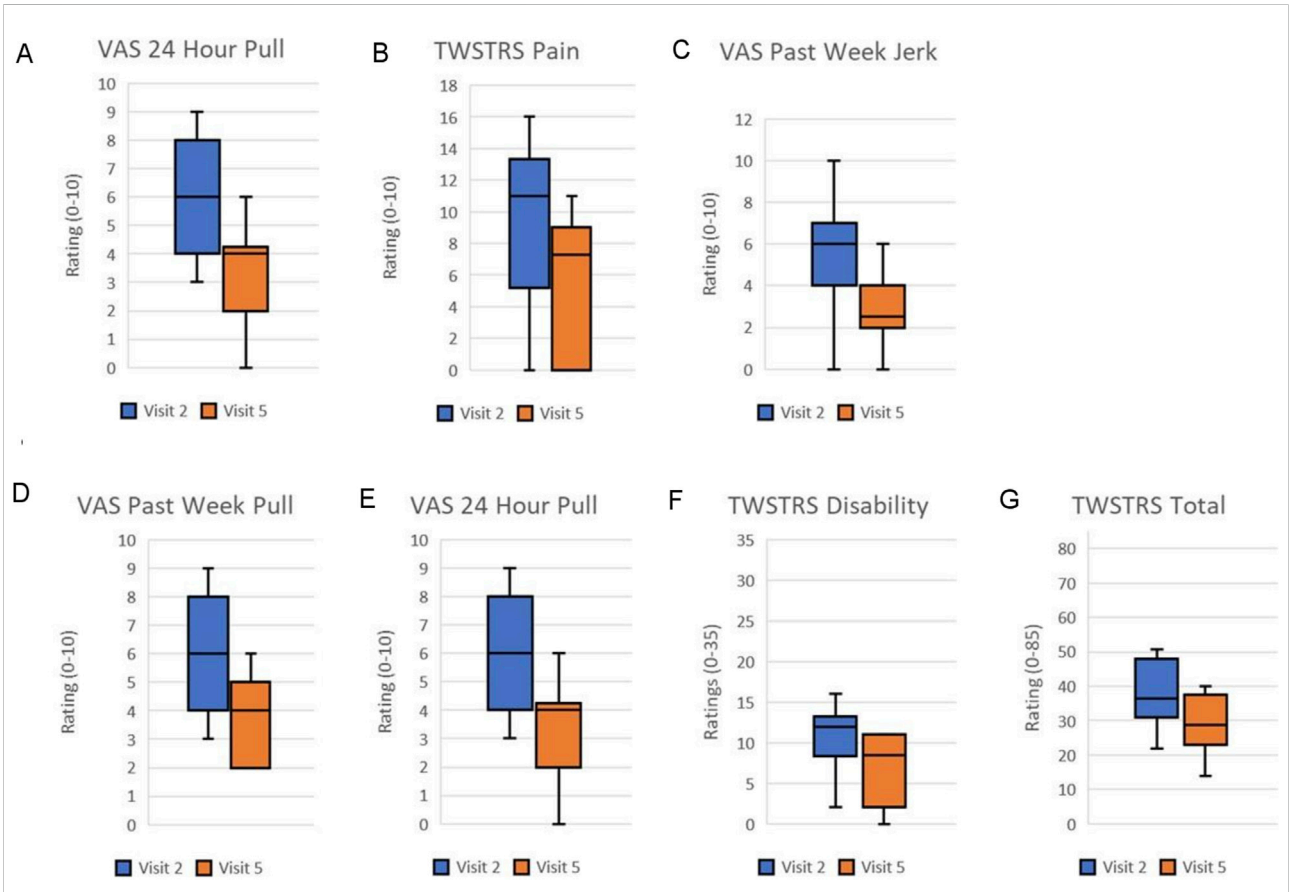

FIGURE 3
Visit 2 (BoNTmin/VBZ dispensing) and Visit 5 (BoNTmin/+VBZ) Comparison. VAS 0–10 scores for **(A)** 24 Hour Pull (p = 0.01), **(B)** 24 Hour Jerk (p = 0.04), **(C)** Past Week Pull (p = 0.002), and **(D)** Past Week Jerk (p = 0.02). TWSTRS Scores for **(E)** Pain (p = 0.05), **(F)** Disability (p = 0.03), and **(G)** Total (p = 0.02).

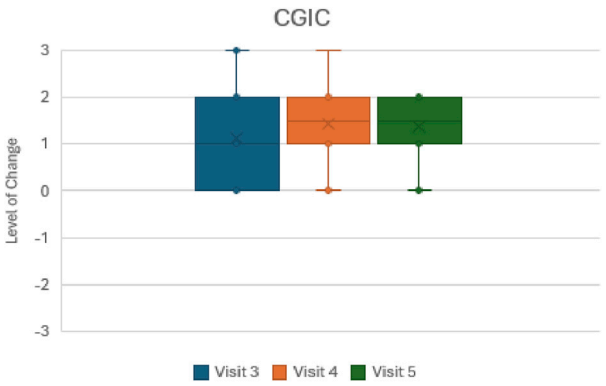

FIGURE 4
Demonstrates the CGIC scale distribution of the ratings across visits 3–5. Mean value at visit 3 was 1.14, visit 4 was 1.42, and visit 5 was 1.35.

Safety

As noted earlier, four participants exited the study early due to fatigue, worsening headaches, hives, and increased neck pulling respectively.

Out of the 14 participants that completed the study successfully, 9 experienced mild adverse effects, with 1 of these also experiencing a serious adverse event of pancreatic cancer deemed unrelated to the study drug. The most common adverse event was fatigue. Table 3 reviews all adverse events reported in the study.

At visit 3, 4 participants elected to stay at 40 mg due to side effects while 10 elected to increase their dose to 80 mg. At visit 4, 2 participants elected to decrease to 40 mg after increasing their dose to 80 mg, therefore, 8 participants remained at the 80 mg dose for the remainder of the study.

TABLE 3 Adverse events.

Adverse event	n (%)	Severity	Relationship	SAE (Y/N)
Worsening dry mouth	1 (5)	Mild	Unlikely related	No
Insomnia	1 (5)	Mild	Unlikely related	No
Vivid dreams	1 (5)	Mild	Unlikely related	No
Frequent urination	1 (5)	Mild	Unlikely related	No
Fatigue	6 (30)	Mild	Possibly related	No
Sleepiness	2 (10)	Mild	Possibly related	No
Off balance	1 (5)	Mild	Unlikely related	No
Jaundice	1 (5)	Mild	Unlikely related	No
Pancreatic cancer	1 (5)	Severe	Not related	Yes
Hair loss	1 (5)	Mild	Possibly related	No
Constipation	1 (5)	Mild	Possibly related	No
Decreased focus	1 (5)	Mild	Possibly related	No
Apathy	1 (5)	Mild	Possibly related	No
Headache/worsening headache	2 (10)	Mild	Possibly related	No
Hives	1 (5)	Mild	Possibly related	No
Increased neck pulling	1 (5)	Mild	Possibly related	No

Discussion

The improvement noted in visit 4 as compared to visit 1 as well as the improvement in Visit 5 as compared to visit 2 demonstrates the role of VBZ when added to ongoing botulinum toxin treatment. In general, CD patients treated with botulinum toxin typically experience re-emergence of symptoms such as abnormal posture, neck pain and limited range of motion (Visit 2). The addition of VBZ to the ongoing botulinum toxin treatment indicated less end of cycle wearing off (Visit 5).

Oral medications are typically used to treat generalized dystonia and botulinum toxins are the primary treatment option for focal dystonia [14]. Increasing oral medications

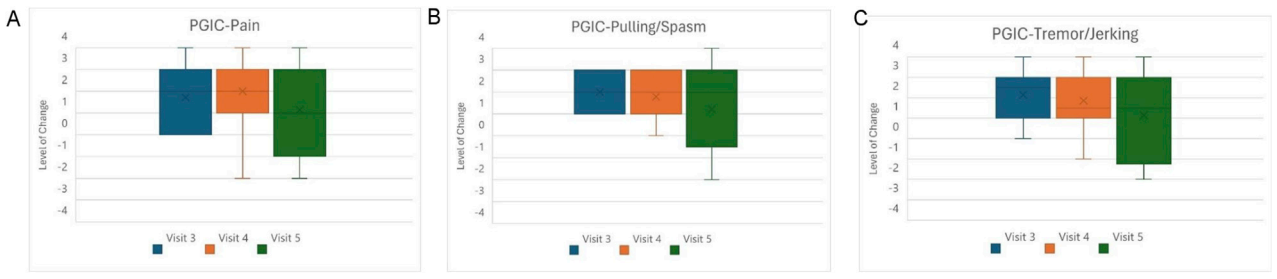

FIGURE 5
(A) Demonstrates the PGIC-pulling and spasm distribution of ratings across visits 3–5. Mean value at visit 3 was 0.76, visit 4 was 1.78, and visit 5 was 1.21. **(B)** shows the PGIC-pain distribution of ratings across visits 3–5. Mean value at visit 3 was 1.71, visit 4 was 2.61, and visit 5 was 1.14. **(C)** shows the PGIC-tremor and jerking distribution of ratings across visit 3–5. The mean value at visit 3 was 2.143, visit 4 was 1.86, and visit 5 was 1.14.

have been studied in the management of focal and generalized dystonia [15]. A case series demonstrated the benefit of dual dopaminergic modulation in cervical dystonia with L-Dopa and Chlorpromazine that medication alone [16]. A case report of clozapine and VBZ in treating cervical dystonia also support the role of modulating dopamine [17]. Another case series recommends that adjunct therapies including oral medications should be considered in patients with refractory CD and residual symptoms after deep brain stimulation [18].

Limitations of the study include the small sample size, the absence of placebo arm, and lack of more detailed data collection (i.e., breakdown of subjects pain, dystonic posturing, and tremor).The single peak dose response demonstrated that the addition of VBZ provides additional benefit when added to individuals receiving stable doses of botulinum toxin. Our study supports the literature that modulating dopamine positively impacts the management of cervical dystonia. It is unique that it combines the use of botulinum toxins and dopamine modulation to achieve an improvement in CD symptoms.

Conclusion

There is a significant lack of efficacious oral medication treatment options for patients living with cervical dystonia. This pilot study is the first to demonstrate the role of avobenzone in combination with botulinum toxin in the management of cervical dystonia. The addition of valbenazine to individuals already receiving injections and the further reduction of symptoms over the last 4 weeks of injection cycle is promising. Furthermore, it would be valuable to explore the benefit of valbenazine over successive injection cycles to see if benefits accrue or plateau. The benefit indicates a role for modulating dopamine hyperactivity in individuals with cervical dystonia. The results are promising and need further study to verify the results including a placebo control arm, a larger sample size and successive cycle of treatment.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ohio University Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SA: project administration, study design, methodology, data collection, data analysis, data interpretation, writing-original draft, writing, review and editing-subsequent drafts. EP: project administration, study design, methodology, data collection, data analysis, data interpretation, writing-original draft, writing, review and editing-subsequent drafts. AW: data analysis, data interpretation, and graphs. LB: writing-original draft, writing, review and editing-subsequent drafts. MT: funding acquisition, supervision, project administration, study design, methodology, data collection, data analysis, data interpretation, writing-original draft, writing, review and editing-subsequent drafts. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The authors declare that no Generative AI was used in the creation of this manuscript.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/dyst.2025.13923/full#supplementary-material

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