Predictors of alcohol responsiveness in dystonia

Johanna Junker, MD, Valerie Brandt, PhD, Brian D. Berman, MD, MS, Marie Vidailhet, MD, Emmanuel Roze, MD, PhD, Anne Weissbach, MD, Cynthia Comella, MD, Irene A. Malaty, MD, Joseph Jankovic, MD, Mark S. LeDoux, MD, PhD, Alfredo Berardelli, MD, Richard Barbano, MD, PhD, Stephen G. Reich, MD, Joel S. Perlmutter, MD, H.A. Jinnah, MD, PhD, and Norbert Brüggemann, MD

Correspondence

Dr. Brüggemann
norbert.brueggemann@
neuro.uni-luebeck.de

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Abstract

Objective

To determine predictors of alcohol responsiveness in a large cohort of patients with dystonia.

Methods

A total of 2,159 participants with dystonia were prospectively enrolled in the cross-sectional Dystonia Coalition multicenter study. Patients with secondary, combined, or confirmed genetic dystonia (total $n = 164$) or unknown alcohol responsiveness ($n = 737$) were excluded. Patients answered a standardized questionnaire and were clinically examined using a standardized video protocol and the Burke-Fahn-Marsden Dystonia Rating Scale. Alcohol responsiveness was determined by patients' self-report.

Results

A total of 1,258 patients with isolated dystonia (mean age: 59.5 ± 12.2 years; 898 women) met the inclusion criteria; 369 patients (29.3%) reported improvement of dystonia after alcohol consumption. Alcohol responsiveness was not related to sex ($p = 0.742$), age ($p = 0.715$), or severity of dystonia ($p = 0.623$). Age at onset was lower in patients who responded to alcohol ($p < 0.001$). Alcohol responsiveness differed across dystonia subgroups (multifocal/generalized > segmental [$p = 0.014$]; cervical and laryngeal > cranial and limb [$p < 0.001$]) and was related to a positive family history of movement disorders ($p = 0.001$), and presence of tremor ($p < 0.001$).

Conclusion

The association of alcohol responsiveness with a positive family history for movement disorders, generalized dystonia, and an earlier age at onset suggests that patients with dystonia who have an underlying genetic contribution may be more likely to respond beneficially to alcohol. The fact that dystonic tremor may respond to alcohol is in keeping with the observation that the intake of GABAergic drugs may have a beneficial effect in a proportion of patients.

From the Institute of Neurogenetics (J. Junker, V.B., A.W., N.B.) and Department of Neurology (J. Junker, N.B.), University of Luebeck, Germany; Department of Psychology (V.B.), Centre for Innovation in Mental Health, University of Southampton, UK; Department of Neurology (B.D.B.), University of Colorado Anschutz Medical Campus, Aurora; Neurology Section (B.D.B.), Denver VA Medical Center, CO; Département de Neurologie (M.V., E.R.), Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris; Sorbonne Universités (M.V.), Pierre Marie Curie Paris-6, Institute of Brain and Spine (ICM), Inserm U 1127, Paris, France; Department of Neurology (C.C.), Rush University Medical Center, Chicago, IL; Department of Neurology (I.A.M.), Center for Movement Disorders and Neurorestoration, University of Florida, Gainesville; Department of Neurology (J. Jankovic), Baylor College of Medicine, Houston, TX; Department of Neurology (M.S.L.), University of Tennessee Health Science Center, Memphis; Neuromed Institute (IRCCS) (A.B.), Pozzilli (IS), and Department of Neurology and Psychiatry, Sapienza University di Roma, Italy; Department of Neurology (R.B.), University of Rochester Medical Center, NY; Department of Neurology (S.G.R.), University of Maryland Medical Center, Baltimore; Department of Neurology (J.S.P.), Washington University in St. Louis, MO; and Department of Neurology and Human Genetics (H.A.J.), Emory University, Atlanta, GA.

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Glossary

BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale; **GABA** = γ -aminobutyric acid.

Dystonia is a movement disorder characterized by involuntary, sustained, or intermittent muscle contractions with resultant abnormal movements and postures. Tremor frequently occurs in patients with dystonia, either in the dystonic body part or remote body regions.^{1,2} Dystonia and tremor are the only motor abnormalities permitted in the diagnostic criteria for isolated forms of dystonia.¹

Some patients with dystonia report substantial improvement with alcohol intake. The exact prevalence of this response within different dystonia groups remains unknown. Small case series suggest that responsiveness to alcohol may be more common in certain forms of dystonia with a specific genetic background or a distinct clinical presentation. In particular, many patients with myoclonus-dystonia report remarkable motor improvement with alcohol,³ which may lead to excessive drinking and alcohol dependency. The alcohol-induced improvement, however, mainly relates to myoclonus in myoclonus-dystonia. Similarly, alcohol intake can ameliorate speech disturbances in spasmodic dysphonia⁴ and in those with laryngeal dystonia due to *TUBB4A* mutations.^{5,6} Patients with isolated generalized or focal hand dystonia also may respond to alcohol.^{7,8}

Given the limited evidence thus far, it remains inconclusive whether alcohol responsiveness relates to the presence of certain clinical variables, such as type of dystonia, a positive family history for movement disorders, or specific phenotypic characteristics, e.g., tremor.

In our study, we prospectively investigated the prevalence of alcohol responsiveness in a large cohort of patients with isolated dystonia. We hypothesized that alcohol responsiveness relates to certain subtypes of dystonia and to the presence of a positive family history, an earlier age at onset, and tremor.

Methods

Participants

Data of the Natural History and Biorepository Project of the Dystonia Coalition clinical database from participants enrolled between January 5, 2011, and August 28, 2015, across 37 clinical sites (United States, Canada, Australia, Germany, France, England, Italy) were used (additional Dystonia Coalition investigators who contributed participants to our study are listed in data available from Dryad [appendix 1, doi.org/10.5061/dryad.hj08j85]). The Dystonia Coalition is a multicenter study of individuals, aged 18 years and older, diagnosed with dystonia (rarediseasesnetwork.org/cms/dystonia). Participants included in the Dystonia Coalition answered a standardized questionnaire and were clinically examined using

a standardized video protocol. Patients receiving botulinum toxin for dystonia were enrolled with an interval of at least 2 months after the last injection. Exclusion criteria for the current study included secondary dystonia, combined dystonia, confirmed mutation in a dystonia-related gene (patients or relatives), medical/neurologic disorders prohibiting the completion of the questionnaire or physical examination, and patients who answered “unknown” regarding alcohol responsiveness.

According to the distribution of dystonic symptoms, the type of primary dystonia was divided into focal, segmental, and multifocal/generalized dystonia (main groups of dystonia). Focal dystonia was further divided into cranial, laryngeal, cervical, and limb dystonia (subgroups of focal dystonia). Cranial dystonia was divided into blepharospasm, upper and lower facial involvement, and oromandibular/lingual dystonia (subgroups of cranial dystonia).

Standard protocol approvals, registrations, and patient consents

Before study enrollment, all participants gave written informed consent for study participation. All clinical sites had study approval by their local ethics committees.

Dystonia Coalition questionnaire

Demographic and clinical data included sex, age, affected body regions, age at onset, disease duration, mutation in dystonia-related genes in study participants or relatives, family history of movement disorders, and presence of other movement disorders including tremor. Alcohol responsiveness was assessed using the question, “Has alcohol relieved the dystonia?” with the answer options “yes,” “no,” or “unknown.”

Video protocol and rating

Standardized videos were recorded in all patients, including examination of speech, voice, swallowing, handwriting, standing, walking, and movement of eyes, neck, arms, hands, legs, and feet.⁹

Videos were evaluated by a neurologist specialized in movement disorders and rated using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS).¹⁰ The BFMDRS is a validated rating scale (range 0–120) for the assessment of dystonia severity. Provoking (scale 0–4) and severity (scale 0–4) factors of 9 different body parts (eyes, mouth, speech/swallowing, neck, right arm, left arm, right leg, left leg, and trunk) were evaluated. For each body part, provoking factor, severity factor, and a weight factor (0.5 or 1) were multiplied.

Statistical analysis

We ran *t* tests against the null hypothesis (null hypothesis: a dystonia group is not significantly responsive to alcohol) to

investigate whether dystonia groups were significantly responsive to alcohol or not at a Bonferroni-corrected $p < 0.005$ to account for 10 comparisons. We then computed χ^2 tests to assess differences in alcohol responsiveness between dystonia subgroups within the 3 types of dystonia ([A] main groups of dystonia, [B] subgroups of focal dystonia, [C] subgroups of cranial dystonia) and sex. To account for multiple comparisons, Bonferroni correction for the 3 types of dystonia was performed ([A] $p \leq 0.017$, [B] $p \leq 0.008$, [C] $p \leq 0.017$).

The association of symptom severity, age, and age at onset of dystonia with alcohol responsiveness was assessed using a binary logistic regression with symptom severity, current age, and age at onset as independent variables and alcohol responsiveness as the dependent variable. Goodness of fit was assessed by Nagelkerke R^2 .

A univariate analysis of variance with age at onset as a covariate was conducted to investigate the effects of a positive family history for movement disorders and the presence of tremor on alcohol responsiveness as the dependent variable.

All tests of significance were 2-sided. The p values ≤ 0.05 were considered significant, unless Bonferroni-corrected. Analyses were run in SPSS Statistics 22 (IBM Corp., Armonk, NY).

Data availability

Anonymized data (study protocol, statistical analysis) will be shared by request from any qualified investigator. Data will be available for 10 years.

Results

Of 2,159 participants, 164 were excluded (secondary dystonia, combined dystonia, confirmed mutation in a dystonia-related gene). Among the 1,995 with isolated dystonia, 737 patients answered the question, "Has alcohol relieved the dystonia?" with "unknown" either because of lack of alcohol consumption or a failure to remember. Because patients with an unknown response to alcohol were excluded, data from 1,258 participants (mean age: 59.5 ± 12.17 years; 898 women [71.4%]) could be analyzed. Of these remaining 1,258 participants, 0.19% of data points were missing. Because of the low number of missing data points (<5%), no imputation technique was used for replacement.

Demographic data of patients are shown in table 1 and data available from Dryad (table 3, doi.org/10.5061/dryad.hj08j85). The majority of patients had focal (78%) and segmental (16.7%) dystonia, and only a minority of patients had multifocal or generalized dystonia (5.3%). The average age at onset of dystonia was 45.3 ± 14.7 years, and the average disease duration was 14.1 ± 12.0 years. Because of the high number of patients with focal forms of dystonia, the mean BFMDRS score was only 7.3 ± 7.5 . Aside from isolated dystonia, more than half of the patients had a dystonic tremor or tremor associated with

dystonia (50.5%). The family history of movement disorders was positive in 32.8% of patients.

Alcohol responsiveness in different dystonia groups

Among the 1,258 patients included, 369 (29.3%) answered the question of alcohol responsiveness with "yes" and 889 (70.7%) with "no."

The t tests against the null hypothesis showed that the main groups of dystonia (multifocal/generalized, segmental, focal) were responsive to alcohol (table 2). Chi-square tests showed different likelihoods of alcohol responsiveness ($\chi^2 = 5.98$, $p = 0.050$), as illustrated in the figure. Patients with multifocal/generalized dystonia showed higher rates of alcohol responsiveness than patients with segmental dystonia ($\chi^2 = 5.99$, $p = 0.014$). Rates of alcohol responsiveness did not differ between multifocal/generalized and focal dystonia ($\chi^2 = 4.03$, $p = 0.045$) and between focal and segmental dystonia ($\chi^2 = 1.34$, $p = 0.247$).

All subgroups of focal dystonia (cranial, laryngeal, cervical, limb) were responsive to alcohol (table 2). Chi-square tests showed different likelihoods of alcohol responsiveness among the subgroups ($\chi^2 = 45.86$, $p < 0.001$), with cervical dystonia (cervical vs cranial: $\chi^2 = 28.29$, $p < 0.001$; cervical vs limb: $\chi^2 = 19.59$, $p < 0.001$) and laryngeal dystonia (laryngeal vs cranial: $\chi^2 = 21.65$, $p < 0.001$; laryngeal vs limb: $\chi^2 = 16.53$, $p < 0.001$) being most responsive (figure). Rates of alcohol responsiveness did not differ between cervical and laryngeal dystonia ($\chi^2 = 0.16$, $p = 0.692$) and between cranial and limb dystonia ($\chi^2 = 0.0$, $p = 0.986$).

The t tests against null hypothesis and χ^2 tests showed that subtypes of cranial dystonia (blepharospasm, upper and lower facial involvement, oromandibular/lingual) differed in response to alcohol ($\chi^2 = 5.99$, $p = 0.05$) with oromandibular/lingual dystonia being most responsive (oromandibular/lingual vs blepharospasm: $\chi^2 = 5.98$, $p = 0.014$), as shown in table 2 and the figure. Rates of alcohol responsiveness did not differ between blepharospasm vs upper and lower facial involvement ($\chi^2 = 0.83$, $p = 0.363$) and between oromandibular/lingual dystonia vs upper and lower facial involvement ($\chi^2 = 1.95$, $p = 0.162$).

Determinants of alcohol responsiveness: Sex, age, age at onset, and dystonia severity

Men and women did not differ in alcohol responsiveness ($\chi^2 = 0.11$, $p = 0.742$). A binary logistic regression analysis with age at onset, current age, and severity of dystonia as independent variables showed that patients with an earlier onset of dystonia were more responsive to alcohol than those with a later onset (Nagelkerke $R^2 = 0.06$, $\chi^2_3 = 46.63$, $p < 0.001$; odds ratio 0.97, Wald[1] = 25.00, $p < 0.001$), whereas current age (odds ratio = 1.00, Wald[1] = 0.13, $p = 0.715$) and severity of dystonia (odds ratio = 1.00, Wald[1] = 0.24, $p = 0.623$) were not associated.

Table 1 Demographic and clinical data of the study cohort

	Data available	All (n = 1,258)	AR (n = 369)	Non-AR (n = 889)	p Value (AR vs non-AR)
Sex	1,258				
Female		898 (71.4)	261 (70.7)	637 (71.7)	
Male		360 (28.6)	108 (29.3)	252 (28.3)	$\chi^2 = 0.11, p = 0.742^a$
Age	1,257	59.5 ± 12.2	56.8 ± 12.6	60.6 ± 11.8	OR = 1.00, $p = 0.715^b$
Age at onset	1,255	45.3 ± 14.7	40.6 ± 14.9	47.3 ± 14.2	OR = 0.97, $p < 0.001^{b,e}$
BFMDRS score	1,052	7.3 ± 7.5	7.8 ± 9.4	7.1 ± 6.5	OR = 1.00, $p = 0.623^b$
Main groups of dystonia	1,255				
Focal		979 (78.0)	286 (78.1)	693 (78.0)	$t_{978} = 20.09, p < 0.001^{c,e}$
Segmental		210 (16.7)	53 (14.5)	157 (17.6)	$t_{209} = 8.4, p < 0.001^{c,e}$
Multifocal/generalized		66 (5.3)	27 (7.4)	39 (4.4)	$t_{65} = 6.71, p < 0.001^{c,e}$
Subgroups of focal dystonia	979				
Cranial		156 (15.9)	20 (7.0)	136 (19.6)	$t_{155} = 4.77, p < 0.001^{c,e}$
Laryngeal		120 (12.3)	44 (15.4)	76 (11.0)	$t_{119} = 8.30, p < 0.001^{c,e}$
Cervical		601 (61.4)	209 (73.1)	392 (56.6)	$t_{600} = 17.89, p < 0.001^{c,e}$
Limb		102 (10.4)	13 (4.5)	89 (12.8)	$t_{101} = 3.84, p < 0.001^{c,e}$
Subgroups of cranial dystonia	156				
Blepharospasmus		77 (49.4)	6 (30)	71 (52.2)	$t_{76} = 2.53, p = 0.013^c$
Upper/lower facial		47 (30.1)	6 (30)	41 (30.2)	$t_{46} = 2.60, p = 0.013^c$
Oromandibular/lingual		32 (20.5)	8 (40)	24 (17.6)	$t_{31} = 3.22, p = 0.003^{c,e}$
Family history	1,249				
Positive		409 (32.8)	155 (42.5)	254 (28.7)	
Negative		801 (64.1)	201 (55.0)	600 (67.9)	$F_{1, 1,198} = 10.98, p = 0.001^{d,e}$
Unknown		39 (3.1)	9 (2.5)	30 (3.4)	
Tremor	1,252				
Yes		632 (50.5)	227 (61.9)	405 (45.8)	$F_{1, 1,198} = 23.92, p < 0.001^{d,e}$
No		620 (49.5)	140 (38.1)	480 (54.2)	

Abbreviations: AR = alcohol responsive; BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale; non-AR = non-alcohol responsive; OR = odds ratio. Data represent mean ± SD or n (%).

^a Chi-square test.

^b Binary logistic regression analysis.

^c *t* Test against the null hypothesis (Bonferroni-corrected significance level: $p \leq 0.005$).

^d Univariate analysis of covariance.

^e Significant.

Determinants of alcohol responsiveness: Family history and tremor

A univariate analysis of covariance, assessing the effects of family history of movement disorders and tremor on alcohol responsiveness with age at onset as a covariate, showed a main effect for the covariate age at onset ($F_{1, 1,198} = 46.68, p < 0.001$), confirming that patients with an earlier onset were more likely responsive to alcohol, a main effect for dystonic tremor, i.e., tremor associated with dystonia ($F_{1, 1,198} = 23.92, p < 0.001$), indicating that patients with tremor were likewise

more often responsive to alcohol, a main effect for family history of movement disorders ($F_{1, 1,198} = 10.98, p = 0.001$), indicating that patients with a family history of movement disorders were more likely to be responsive, and no interaction between having a family history of movement disorders and tremor ($F_{1, 1,198} = 1.8, p = 0.18$).

Frequencies of family history of movement disorders among different dystonia types are provided in data available from Dryad (table 3, doi.org/10.5061/dryad.hj08j85).

Table 2 Alcohol responsiveness among different types of dystonia

Main groups of dystonia				
	Focal (n = 979)	Segmental (n = 210)	Multifocal/generalized (n = 66)	
AR, n (%)	286 (29.2)	53 (25.2)	27 (40.9)	
Non-AR, n (%)	693 (70.8)	157 (74.8)	39 (59.1)	
Mean (SD)	0.29 (0.46)	0.25 (0.44)	0.41 (0.50)	
t Test against 0 (p)	20.09 (<0.001) ^a	8.4 (<0.001) ^a	6.71 (<0.001) ^a	
Subgroups of focal dystonia				
	Cranial (n = 156)	Laryngeal (n = 120)	Cervical (n = 601)	Limb (n = 102)
AR, n (%)	20 (12.8)	44 (36.7)	209 (34.8)	13 (12.7)
Non-AR, n (%)	136 (87.2)	76 (63.3)	392 (65.2)	89 (87.3)
Mean (SD)	0.13 (0.34)	0.37 (0.48)	0.35 (0.48)	0.13 (0.34)
t Test against 0 (p)	4.77 (<0.001) ^a	8.30 (<0.001) ^a	17.89 (<0.001) ^a	3.84 (<0.001) ^a
Subgroups of cranial dystonia				
	Blepharospasm (n = 77)	Upper/lower facial (n = 47)	Oromandibular/lingual (n = 32)	
AR, n (%)	6 (7.8)	6 (12.8)	8 (25)	
Non-AR, n (%)	71 (92.2)	41 (87.2)	24 (75)	
Mean (SD)	0.08 (0.27)	0.13 (0.34)	0.25 (0.44)	
t Test against 0 (p)	2.53 (0.013)	2.60 (0.013)	3.22 (0.003) ^a	

Abbreviations: AR = alcohol responsive; non-AR = non-alcohol responsive.
t Tests against the null hypothesis; Bonferroni-corrected significance level: $p \leq 0.005$.
^a Significant.

Discussion

In this large, international, multicenter study including datasets of more than 1,200 patients with isolated dystonia, almost a third reported an improvement of their motor symptoms due to consumption of alcohol. Alcohol responsiveness did

not relate to sex, current age, or severity of dystonia as measured by the BFMDRS.

The association of alcohol responsiveness and a positive family history for movement disorders suggests that dystonia with an underlying genetic contribution may have a greater

Figure Degree of alcohol responsiveness across different dystonia groups

Patients with multifocal/generalized dystonia had a greater likelihood of response than patients with segmental dystonia (A). Among subgroups of focal dystonia, patients with either cervical or laryngeal dystonia had a greater likelihood of response than patients with limb or cranial dystonia (B). Among the subgroups of cranial dystonia, patients with oromandibular/lingual dystonia responded more frequently than patients with blepharospasm (C). *Bonferroni-corrected p : (A) $p \leq 0.017$, (B) $p \leq 0.008$, (C) $p \leq 0.017$; *** $p < 0.001$.

likelihood of responding to alcohol, as alcohol responsiveness appears to be more frequent in genetic forms of dystonia, e.g., in DYT-TUBB4A and DYT-SGCE.^{3,6} Moreover, subgroup analyses showed greater chance of response to alcohol in patients with more widespread dystonia, i.e., generalized and multifocal dystonia (41% of patients) and lowest chance of response in blepharospasm (8% of patients). Within the subgroup of focal dystonia, patients with laryngeal (37%) and cervical dystonia (35%) showed the highest rates of alcohol responsiveness. In addition, earlier age at onset of dystonia indicated a greater chance of responding to alcohol. Patients with genetic dystonias often have an earlier age at onset and are more likely to develop generalized or multifocal dystonia,^{4,6,7,11–13} which supports the notion that alcohol responsiveness appears more frequently in dystonia with underlying heritability. In contrast, patients with blepharospasm typically have an onset late in life and environmental factors are much more likely to contribute to dystonia than genetic factors.^{14,15} These results may implicate further genes being associated with alcohol-responsive dystonia, which may give rise to further genetic investigations.

Patients with dystonic tremor or tremor associated with dystonia had a higher chance of symptom relief after alcohol consumption than patients without tremor. This is consistent with observations that essential tremor decreases with orally administered ethanol in about 50% of patients.^{16–18} A significant role of the cerebellum in the pathophysiology of both essential tremor and dystonia has recently been postulated and related to a decreased Purkinje cell density.^{19,20} Such pathophysiologic similarities of dystonic and essential tremor could be linked to tremor improvement with alcohol intake in both diseases. Our results thus suggest that alcohol responsiveness may not be a reliable marker to support a diagnosis of essential tremor over a diagnosis of dystonic tremor. It also raises the question whether alcohol causes global improvement of tremor per se or whether the improvement is attributed to reduced dystonia. In this context, patients with laryngeal dystonia reported relief of dystonic symptoms after alcohol ingestion, which was not associated with the presence of tremor, arguing for an independent effect of alcohol on dystonia.⁴

The underlying biochemical mechanisms of the dystonia-improving effects of alcohol remain unknown.²¹ A possible explanation concerns interactions with GABAergic neurotransmission. GABA_A (γ -aminobutyric acid type A) receptor dysfunction in the striatum, primary motor and premotor cortices, somatosensory cortex, and the cerebellum may contribute to dystonic manifestations.^{20,22–26} Ethanol enhances GABAergic neurotransmission in the brain^{27–29} and could potentially improve dystonia by overcoming dystonia-related disinhibition of the somatosensory network. Similarly, other GABA-enhancing substances such as benzodiazepines, zonisamide, and sodium oxybate produce similar effects as alcohol.^{27,30–34} In particular, sodium oxybate effectively reduced dystonia in patients with alcohol-responsive laryngeal

dystonia.³⁵ However, antidystonic drugs often have only a partial effect in a minority of patients,³⁶ which is in keeping with our observation that only 30% of patients showed a response to alcohol.

Aside from a possible association of alcohol responsiveness and underlying heritability, the individual perception of improvement of dystonia also could be influenced by the anxiolytic properties of alcohol.^{27,37} Patients with cervical and laryngeal onset exhibit the highest degree of anxiety across patients with isolated dystonia with laryngeal onset having the highest levels of social anxiety.³⁸ Thus, reduction of anxiety through alcohol could potentially reduce patients' concerns about dystonia or improve motor symptoms as dystonia usually increases with emotional stress.^{12,39} This is in keeping with our observation that patients with cervical and laryngeal dystonia showed the highest chance of response to alcohol among patients with focal dystonias.

Our cross-sectional study had certain limitations: information on alcohol responsiveness was based on self-assessment with limited response options (yes, no, unknown). The degree of improvement could thus not be determined since the response was not verified by direct observation. Even though this international multicenter study is the largest of its kind, certain dystonia subgroups had small sample sizes. This limits the confidence on the findings in generalized, multifocal, oromandibular, and lingual dystonia. Future studies are warranted to validate the effects of alcohol on dystonia and dystonic tremor and to additionally address the alcohol-dependent reduction of anxiety and pain.

The present study revealed clinical characteristics in patients with dystonia related to alcohol responsiveness. These characteristics include type of dystonia, age at onset, a positive family history for movement disorders, and dystonic tremor, i.e., tremor associated with dystonia. These new insights may allow clinicians to stratify clinical trials of new therapies by identifying patients who may better respond to GABAergic drugs. Our findings could be a starting point to better understand the various pharmacologic features and underlying disease mechanisms of dystonia in order to develop specific therapies for subgroups of patients.

Author contributions

Johanna Junker: acquisition of data, study concept and design, statistical analysis, analysis and interpretation of data, drafting of manuscript. Valerie Brandt: statistical analysis, critical revision of manuscript for intellectual content. Brian D. Berman, Marie Vidailhet, Emmanuel Roze, Anne Weissbach, Cynthia Comella, Irene A. Malaty, Joseph Jankovic, Mark S. LeDoux, Alfredo Berardelli, Richard Barbano, Stephen G. Reich, Joel S. Perlmuter, and H.A. Jinnah: acquisition of data, critical revision of manuscript for intellectual content. Norbert Brüggemann: study concept and design, analysis and interpretation of data, study supervision, critical revision of manuscript for intellectual content.

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Disclosure

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