

## Quality of life in isolated dystonia – non-motor manifestations matter

Johanna Junker, MD<sup>1,2</sup>, Brian D. Berman, MD, MS<sup>3,4</sup>, James Hall, Dphil<sup>5</sup>, Deena Wahba, MS<sup>6</sup>, Valerie Brandt, PhD<sup>7</sup>, Joel S. Perlmutter, MD<sup>8</sup>, Joseph Jankovic, MD<sup>9</sup>, Irene A. Malaty, MD<sup>10</sup>, Aparna Wagle Shukla, MD<sup>10</sup>, Stephen G. Reich, MD<sup>11</sup>, Alberto J. Espay, MD<sup>12</sup>, Kevin R. Duque, MD<sup>12</sup>, Neepa Patel, MD<sup>13</sup>, Emmanuel Roze, MD, PhD<sup>14,15</sup>, Marie Vidailhet, MD<sup>14,15</sup>, H. A. Jinnah, MD, PhD<sup>16</sup>, Norbert Brüggemann, MD<sup>1,2</sup>

<sup>1</sup> Institute of Neurogenetics, University of Luebeck, Luebeck, Germany

<sup>2</sup> Department of Neurology, University of Luebeck, Luebeck, Germany

<sup>3</sup> Department of Neurology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

<sup>4</sup> Neurology Section, Denver VA Medical Center, Denver, CO, USA

<sup>5</sup> Southampton Education School, University of Southampton, UK

<sup>6</sup> BayCare Laboratories, Tampa, FL, USA

<sup>7</sup> School of Psychology, Centre for Innovation in Mental Health, University of Southampton, UK

<sup>8</sup> Departments of Neurology, Radiology, Neuroscience, Physical Therapy & Occupational Therapy, Washington University in St. Louis, St. Louis, MO, USA

<sup>9</sup> Parkinsons' Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas, USA

<sup>10</sup> Department of Neurology, Fixel Institute for Neurologic Disorders, University of Florida, Gainesville, Florida, USA

<sup>11</sup> Department of Neurology, University of Maryland, School of Medicine, Baltimore, MD, USA

<sup>12</sup> Department of Neurology, University of Cincinnati, Cincinnati, OH, USA

<sup>13</sup> Department of Neurology, Henry Ford Hospital West Bloomfield, MI, USA

<sup>14</sup> AP-HP, Hopital de la Pitie-Salpetriere, Departement de Neurologie, Paris, France

<sup>15</sup> Sorbonne Universités, Institut du Cerveau\_ Paris Brain Institute-ICM, INSERM 1127, CNRS 7225, Paris, France

<sup>16</sup> Department of Neurology and Human Genetics, Emory University, Atlanta, GA, USA

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**Corresponding Author:**

Norbert Brüggemann, MD

Dept. of Neurology and Institute of Neurogenetics, University of Lübeck

Ratzeburger Allee 160

Lübeck, SH, 23538, Germany

Phone +49-451-500 43401

Fax +49-451-500 43404

[norbert.brueggemann@neuro.uni-luebeck.de](mailto:norbert.brueggemann@neuro.uni-luebeck.de)

Johanna Junker	<a href="mailto:johanna.junker@neuro.uni-luebeck.de">johanna.junker@neuro.uni-luebeck.de</a>
Brian D. Berman	<a href="mailto:brian.berman@cuanschutz.edu">brian.berman@cuanschutz.edu</a>
James Hall	<a href="mailto:J.E.Hall@soton.ac.uk">J.E.Hall@soton.ac.uk</a>
Deena Wahba	<a href="mailto:dwwahba@gmail.com">dwwahba@gmail.com</a>
Valerie Brandt	<a href="mailto:V.C.Brandt@soton.ac.uk">V.C.Brandt@soton.ac.uk</a>
Joel S. Perlmutter	<a href="mailto:perlmutterjoel@wustl.edu">perlmutterjoel@wustl.edu</a>
Joseph Jankovic	<a href="mailto:josephj@bcm.edu">josephj@bcm.edu</a>
Irene A. Malaty	<a href="mailto:irene.malaty@neurology.ufl.edu">irene.malaty@neurology.ufl.edu</a>
Aparna Wagle Shukla	<a href="mailto:aparna.shukla@neurology.ufl.edu">aparna.shukla@neurology.ufl.edu</a>
Stephen G. Reich	<a href="mailto:SReich@som.umaryland.edu">SReich@som.umaryland.edu</a>
Alberto J. Espay	<a href="mailto:alberto.espay@uc.edu">alberto.espay@uc.edu</a>
Kevin R. Duque	<a href="mailto:duqueykr@ucmail.uc.edu">duqueykr@ucmail.uc.edu</a>
Neepa Patel	<a href="mailto:npatel20@hfhs.org">npatel20@hfhs.org</a>
Emmanuel Roze	<a href="mailto:emmanuel.flamand-roze@aphp.fr">emmanuel.flamand-roze@aphp.fr</a>
Marie Vidailhet	<a href="mailto:marie.vidailhet@aphp.fr">marie.vidailhet@aphp.fr</a>
H. A. Jinnah	<a href="mailto:hjinnah@emory.edu">hjinnah@emory.edu</a>

**Co-investigators:** see supplementary file

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## ABSTRACT

**Objective:** To evaluate the relationship between health-related quality of life (HR-QoL) and both physical and psychiatric factors in a large, international, multicenter cohort of isolated dystonia patients, the Dystonia Coalition.

**Methods:** Natural history data from 603 patients with isolated dystonia (median age 57 years (IQR: 48-64 years), 67.0% female) were prospectively acquired and analyzed. HR-QoL (RAND 36-Item Health Survey), severity of depressive symptoms, **generalized** anxiety (Hospital Anxiety and Depression Scale) and social anxiety (Liebowitz Social Anxiety Scale) were assessed. Dystonia severity (Burke-Fahn-Marsden Dystonia Rating Scale) and dystonic tremor were examined. Statistical predictors of HR-QoL were calculated using saturated path analysis.

**Results:** Reduced HR-QoL was strongly associated with the degree of depressive symptoms and **generalized** and social anxiety (8/8 RAND36 subscales,  $p \leq .001$ ). Increased dystonia severity was associated with worse physical functioning, physical and emotional role functioning, and social functioning (all  $p \leq .001$ ). The presence of tremor correlated with worse physical functioning and pain (all  $p \leq .006$ ). Younger age was associated with reduced emotional well-being and vitality (all  $p \leq .006$ ). There were no HR-QoL differences between sexes.

**Conclusion:** HR-QoL in isolated dystonia is strongly associated with psychiatric and physical features. While current standard of care focus on motor aspects of dystonia, comprehensive care should address both physical and mental aspects of health.

## INTRODUCTION

Health-related quality of life (HR-QoL) is reduced in patients with dystonia compared to population-based samples.<sup>1-4</sup> HR-QoL in dystonia is not only determined by motor symptoms (MS) including dystonia severity and dystonic tremor but also by non-motor symptoms (NMS), i.e. depression, anxiety, social phobia, low self-esteem and pain.<sup>3,5</sup> NMS are frequent in dystonia in comparison to population-based samples, which have an annual prevalence of 7% for depression,<sup>6</sup> 1-6% for generalized anxiety disorder (GAD)<sup>7-9</sup> and 2-8% for social anxiety disorder (SAD).<sup>9,10</sup> The point prevalence in dystonia is 16-48% for depression, 20-50% for GAD and 40% for SAD.<sup>3, 5, 11-14</sup> The relationship between MS and NMS is poorly understood, i.e. to which extent NMS are secondary due to MS or a result of impaired neuronal processing.<sup>15</sup>

Previous studies in dystonia aimed to reveal the relationship of HR-QoL with MS and NMS.<sup>15-17</sup> Their significance, however, has been limited due to relatively small sample sizes and methodological differences for example between self-evaluation of dystonia severity vs. rating of dystonia by an experienced investigator.<sup>15-17</sup> Thus, no systematic analysis of the influence of MS and NMS severity on HR-QoL has yet been performed in a comprehensive dystonia cohort. Here, we analyzed data from the Dystonia Coalition cohort, a large prospectively investigated and international sample of isolated dystonia patients, and hypothesized that psychiatric manifestations have a higher impact on HR-QoL than dystonia severity and tremor. Mental health of dystonia patients and its overall burden on HR-QoL may not be well addressed since dystonia treatment mainly focuses on the motor aspects of the disease.

## METHODS

### Participants

The analysis included participants' data from baseline assessment of the Natural History Project of the Dystonia Coalition clinical database enrolled between 12 January 2011 and 3 November 2017 across 36 clinical sites (USA, Canada, Australia, Germany, France, Italy). Additional Dystonia Coalition investigators that contributed subjects to the study are listed in Supplementary File. The Dystonia Coalition is a multicenter study of isolated dystonia patients, aged 18 years and older, and the Natural History Project includes patients with dystonia onset no more than five years prior to study enrollment (<https://www.rarediseasesnetwork.org/cms/dystonia>).

Participants answered a standardized questionnaire and were clinically examined using a standardized protocol. Dystonia patients with botulinum toxin (BoNT) treatment were enrolled when symptoms returned. This usually meant they were enrolled 3 months after treatment, but never less than two months after treatment. Exclusion criteria were secondary and combined dystonia and medical/neurological conditions confounding diagnoses or precluding a complete assessment. For the current study a small group of patients with a confirmed mutation in a dystonia-related gene were excluded (n=12) as certain monogenic forms, e.g. SGCE-related dystonia, exhibit a specific neuropsychiatric profile and are thus accompanied by a high burden of NMS.<sup>18</sup>

Classification of dystonia referring to body distribution was conducted according to Albanese et al.<sup>19</sup> Type of dystonia was divided into focal, segmental, multifocal and generalized dystonia. Focal dystonia was further divided into blepharospasm, oromandibular/lingual, laryngeal, cervical and limb dystonia.

## **Standard Protocol Approvals and Patient Consents**

All participants gave written informed consent for study participation prior to study enrollment. The study was approved by the local ethics committees of all clinical sites.

## **Questionnaire and Rating Scales**

HR-QoL and NMS were evaluated by generic, validated and widely used rating scales (RAND 36-Item Health Survey, Hospital Anxiety and Depression Scale, Liebowitz Social Anxiety Scale) to allow for comparison with other dystonia and movement disorder studies.<sup>20-22</sup>

### Dystonia Coalition Questionnaire

Demographic and clinical data included sex, age, affected body regions, the presence of other movement disorders including tremor, age at onset, disease duration, medical treatment for dystonia, medical history and mutations in dystonia-related genes.

### RAND 36-Item Health Survey

HR-QoL was evaluated using the RAND 36-Item Health Survey 1.0. The RAND 36 is a generic quality of life questionnaire to measure physical and mental well-being, relies upon patient self-reporting, and was developed in the Medical Outcome Study.<sup>20</sup> It contains 36 questions representing the following eight subscales: general health, physical functioning, role limitations due to physical health problems, pain, energy/fatigue, emotional well-being, role limitations due to emotional problems and social functioning. The questions are rated on a Likert Scale with up to six response options and seven questions are answered with yes or no. Original response categories are recoded to values of a 0 to 100% range and the items of each of the 8 subscales are averaged. A high score represents a better health state. The

RAND 36-Item Health Survey 1.0 and the 36-Item Short Form Survey (SF-36) include the same items, while the scoring algorithm is different regarding the general health and pain scales.<sup>23</sup> The scoring algorithm of the RAND 36-Item Health Survey 1.0 was used in this study.

#### Hospital Anxiety and Depression Scale (HADS)

Severity of **generalized** anxiety and depressive symptoms was assessed by the self-reported Hospital Anxiety and Depression Scale version 4.<sup>21</sup> Each of the two subscales (HADS-A, HADS-D) contain seven questions rated on a 4-point scale (0-3), each subscale yielding score ranging from 0 to 21. Standard scale cut-offs indicated the presence of depression and anxiety (HADS-A > 7, HADS-D > 7).

#### Liebowitz Social Anxiety Scale (LSAS)

The self-reported LSAS is a 24-item scale divided into two subscales assessing fear/anxiety concerning performance and pertaining to social situations as well as avoidance behavior.<sup>22</sup> The 24 items of the two subscales are rated on a Likert Scale from 0 to 3 yielding a maximum sum score of 144. The presence of social anxiety was indicated by a standard scale cut-off > 30.

#### **Examination protocol and rating**

Standardized examination of all patients included evaluation of eyes, mouth, tongue, neck, arms, hands, legs and feet and the examination of speech, voice, swallowing, handwriting, standing and walking.<sup>24</sup> A movement disorder neurologist evaluated dystonia severity across different body regions using the validated Burke-Fahn-Marsden Dystonia Rating Scale

(BFMDRS).<sup>25</sup> Tremor was assessed by observing all body regions for the occurrence of tremor regardless of its amplitude, frequency or regularity. The BFMDRS evaluates provoking (scale 0-4) and severity factors (scale 0-4) of nine different body parts (eyes, mouth, speech/swallowing, neck, right arm, left arm, right leg, left leg, trunk). For each body part, provoking factor, severity factor and a weight factor (0.5 or 1) were multiplied yielding score ranges from 0 to 120, with higher scores indicating more severe dystonia.

### **Statistical analysis**

To analyze the relationship between MS and NMS with HR-QoL, simultaneously estimated bivariate correlations were obtained from a saturated path analysis performed in MPlus version 7.4.<sup>26</sup> The eight subscales of the RAND 36-Item Health Survey, the three NMS scores (HADS-D, HADS-A, LSAS), and the two MS factors (BFMDRS, tremor (yes/no)) were entered into the model, as well as age and sex to control for their effects. The Full Information Maximum Likelihood (FIML) statistical procedure was used for replacement of missing values in the path analysis that was undertaken. Bonferroni-corrected alphas were calculated to adjust for multiple comparisons (simultaneous correlations), and P-values  $\leq 0.006$  were considered significant.

Differences regarding the severity of NMS between patients with and without antidepressants were assessed using t-tests for independent samples. All tests of significance were two-sided. Bonferroni-corrected alphas  $\leq 0.017$  were considered significant.

## **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**

Out of 615 participants, 12 were excluded due to secondary or combined dystonia or a confirmed mutation in a dystonia-related gene. Of the remaining 603 isolated dystonia patients, 1.5% of data points were missing.

The majority of patients were female (67.0%, 404/603). The median age at baseline examination was 57 years (IQR: 48-64 years), and the median age at dystonia onset 54 years (IQR: 45-61 years). Table 1 displays mean BFMDRS scores, the ratio of patients with tremor, mean total scores of RAND 36-Item Health Survey, HADS-D, HADS-A and LSAS as well as the ratio of patients with symptoms of a depression (HADS-D > 7), GAD (HADS-A > 7) and SAD (LSAS > 30). In detail, symptoms of depression were found in 22%, symptoms of GAD in 37% and SAD in 44% of patients.

**Table 1.** Clinical data of the study cohort

	HR-QoL	Depression	Generalized Anxiety	Social Anxiety	BFMDRS	Tremor
<b>All (n=603)</b>	63.6 ± 21.8	21.5% (127/ 591) 4.6 ± 4.0	36.7% (217/591) 6.4 ± 4.2	44.3% (262/591) 32.1 ± 26.0	6.7 ± 5.0	43% (259/603)
<b>Main groups of dystonia</b>						
<b>focal (n=373)</b>	66.3 ± 21.8	20.0 % (73/365) 4.4 ± 4.0	37.3 % (136/365) 6.4 ± 4.1	41.5% (152/366) 30.9 ± 25.4	4.4 ± 2.4	44.0 % (164/373)
<b>segmental (n=171)</b>	58.0 ± 21.0	24.6% (41/167) 5.4 ± 4.1	36.5 % (61/167) 6.7 ± 4.2	55.1% (92/167) 36.8 ± 26.7	9.8 ± 5.3	39.8% (68/171)
<b>multifocal (n=49)</b>	64.4 ± 20.9	20.4% (10/49) 3.9 ± 3.3	30.6% (15/49) 5.3 ± 4.2	30.6% (15/49) 25.9 ± 24.7	9.5 ± 4.4	42.9% (21/49)
<b>generalized (n=10)</b>	58.1 ± 24.9	30% (3/10) 5.0 ± 4.4	50% (5/10) 7.3 ± 5.3	33.3% (3/9) 29.4 ± 34.3	21.4 ± 9.4	60% (6/10)
<b>Subgroups of focal dystonia</b>						
<b>blepharospasm (n=41)</b>	70.8 ± 20.3	19.5% (8/41) 4.3 ± 4.2	24.4% (10/41) 5.3 ± 4.1	19.5% (8/41) 24.2 ± 25.8	4.6 ± 2.3	14.6 % (6/41)
<b>oromandibular /lingual (n=22)</b>	67.7 ± 19.9	18.2% (4/22) 4.7 ± 4.0	22.7% (5/22) 5.5 ± 3.5	36.4% (8/22) 27.9 ± 20.0	3.8 ± 3.0	27.3% (6/22)
<b>laryngeal (n=30)</b>	77.1 ± 15.6	13.3% (4/30) 3.1 ± 3.1	46.7% (14/30) 7.8 ± 4.3	66.7% (20/30) 40.7 ± 23.6	3.1 ± 1.8	33.3% (10/30)
<b>cervical (n=227)</b>	62.3 ± 22.6	23.2% (51/220) 4.7 ± 4.1	41.8% (92/220) 6.8 ± 4.2	45.0% (99/220) 33.1 ± 26.8	4.7 ± 2.3	57.3% (130/227)
<b>limb (n=53)</b>	73.1 ± 18.9	11.5% (6/52) 3.4 ± 3.3	28.8% (15/52) 5.4 ± 3.3	32.1% (17/53) 22.8 ± 17.8	3.8 ± 2.5	22.6% (12/53)

With regard to therapy, 68.0% (410/603) were treated with BoNT, 39.5% (238/603) with oral anti-dystonic drugs (anticholinergics, benzodiazepines, non-benzo hypnotics, dopaminergics, antidopaminergics, muscle relaxants) and 19.1% with antidepressants. The group of patients with antidepressants (depression:  $6.3 \pm 4.3$  vs.  $4.2 \pm 3.8$  (M  $\pm$  SD),  $t(589) = -5.1$ ,  $p < 0.000$ ; GAD:  $8.2 \pm 4.2$  vs.  $6.0 \pm 4.0$  (M  $\pm$  SD),  $t(589) = -5.3$ ,  $p < 0.000$ ; SAD:  $38.6 \pm 30.0$  vs.  $30.6 \pm 24.7$  (M  $\pm$  SD),  $t(589) = -3.0$ ,  $p = 0.003$ ) exhibited higher depression and anxiety scores. None of the patients had deep brain stimulation, whereas 0.8% of patients had previously received other surgical treatment for dystonia (myectomy for blepharospasm or spasmodic dysphonia (n=3), selective denervation for cervical dystonia (n=2)).

#### **Influence of MS and NMS on HR-QoL in dystonia**

The results of the path analysis with numerical estimates as indicators of the strength of the relationships between the eight HR-QoL subscales (RAND 36-Item Health Survey) and dystonia severity (BFMDRS), tremor, severity of depressive symptoms (HADS-D), GAD (HADS-A) and SAD (LSAS), as well as age at examination and sex are displayed in Table 2 and Figure 1. Lower HR-QoL of all eight subscales related to more severe depressive symptoms, GAD and SAD (all  $p \leq .001$ ). Depressive symptoms presented with highest (-0.47 up to -0.72) and social anxiety with lowest estimates (-0.23 up to -0.42). Higher dystonia severity was associated with lower physical functioning, physical and emotional role functioning, and social functioning (all  $p \leq .001$ ), and the presence of tremor was associated with lower HR-QoL regarding physical functioning and pain (all  $p \leq .006$ ). Both dystonia severity and tremor presented low estimates (-0.09 up to -0.24). Younger age was associated with reduced emotional well-being and vitality (all  $p \leq .006$ , estimates 0.13 to 0.15). Sex was not associated with any differences in HR-QoL subscales.

**Table 2.** Simultaneously estimated bivariate correlations obtained from a saturated path analysis

Health-Related Quality of Life subscale	Dystonia Severity	Tremor	Depression	Generalized Anxiety	Social Anxiety	Age	Sex
<b>General Health</b>	-0.09 (-0.17 to -0.01)	-0.05 (-0.13 to 0.03)	-0.50*** (-0.57 to -0.44)	-0.40*** (-0.47 to -0.33)	-0.31*** (-0.39 to -0.22)	0.07 (-0.01 to 0.15)	-0.04 (-0.12 to 0.04)
<b>Physical Functioning</b>	-0.14*** (-0.22 to -0.06)	-0.14*** (-0.22 to -0.06)	-0.47*** (-0.54 to -0.4)	-0.27*** (-0.35 to -0.18)	-0.27*** (-0.36 to -0.18)	-0.07 (-0.15 to 0.01)	-0.07 (-0.15 to 0.002)
<b>Physical Role Functioning</b>	-0.24*** (-0.32 to -0.16)	-0.01 (-0.09 to 0.07)	-0.49*** (-0.55 to -0.43)	-0.35*** (-0.42 to -0.28)	-0.26*** (-0.34 to -0.2)	0.08 (0.003 to 0.16)	-0.06 (-0.14 to 0.02)
<b>Pain</b>	-0.10 (-0.19 to -0.001)	-0.11** (-0.19 to -0.03)	-0.52*** (-0.58 to -0.45)	-0.38*** (-0.46 to -0.31)	-0.23*** (-0.32 to -0.14)	0.11 (0.03 to 0.2)	-0.07 (-0.15 to 0.01)
<b>Energy/Fatigue</b>	-0.09 (-0.17 to -0.01)	-0.09 (-0.18 to -0.01)	-0.66*** (-0.71 to -0.61)	-0.45*** (-0.51 to -0.38)	-0.34*** (-0.41 to -0.27)	0.13** (0.05 to 0.21)	-0.05 (-0.13 to 0.03)
<b>Emotional Well-being</b>	-0.11 (-0.2 to -0.02)	-0.002 (-0.08 to 0.08)	-0.72*** (-0.76 to -0.67)	-0.68*** (-0.72 to -0.63)	-0.41*** (-0.49 to -0.33)	0.15*** (0.07 to 0.22)	0.01 (-0.07 to 0.09)
<b>Emotional Role Functioning</b>	-0.17*** (-0.26 to -0.09)	0.02 (-0.06 to 0.1)	-0.49*** (-0.56 to -0.42)	-0.42*** (-0.48 to -0.35)	-0.32*** (-0.4 to -0.24)	0.11 (0.03 to 0.19)	0.01 (-0.07 to 0.09)
<b>Social Functioning</b>	-0.23*** (-0.32 to -0.15)	-0.004 (-0.09 to 0.08)	-0.67*** (-0.72 to -0.62)	-0.44*** (-0.5 to -0.37)	-0.42*** (-0.5 to -0.35)	0.10 (0.02 to 0.18)	0.05 (-0.03 to 0.14)

## DISCUSSION

Symptoms of depression, GAD and SAD are related to worse HR-QoL in dystonia patients in the large international Dystonia Coalition cohort. We found an additional association of HR-QoL with dystonia severity, tremor and age at examination. Twenty percent of our patients were treated with antidepressants. The degree of underlying depressive symptoms and anxiety may thus have been underestimated.

Our results are in keeping with previous studies in smaller samples of patients with dystonia, which have already indicated that depression, GAD, low self-esteem, embarrassment and acceptance of illness are important determinants of HR-QoL.<sup>3 16 17 27 28</sup> Motor severity was, however, not as strongly associated with HR-QoL in our study. The weaker association with

motor severity may be due to the fact that we used the BFMDRS to assess dystonia severity which is a validated<sup>25</sup> and commonly used rating scale but it may not be sensitive enough for focal dystonias. In keeping with this notion, most patients had focal or segmental dystonia in our sample whereas generalized (10/603) and multifocal (49/603) dystonias were less common. Other studies have also found a stronger relationship of QoL with NMS than with MS but this may again be attributable to the heterogeneity of dystonia subtypes in different cohorts and especially in those with smaller sample sizes and the use of different rating scales (BFMDRS, TWSTRS, Tsui score, UDRS).<sup>3 11 27</sup> Furthermore, the examination of patients under BoNT treatment at different time intervals limits the comparability of results. Of note, almost 70% of our patients were treated with BoNT about three months prior to the examination, indicating that dystonia severity may have been potentially higher in some patients without long-term BoNT therapy<sup>29</sup> and may have resulted in stronger associations with lower HR-QoL. Thus, it is conceivable that the impact of MS severity in our and previous studies may be lessened by the availability and ongoing utilization of effective treatments as BoNT and DBS with positive long-term effects on HR-QoL,<sup>3 30</sup> as compared to the potentially less uniform implementation of treatments for the NMS. MS and MS-related pain should of course be treated to improve and stabilize HR-QoL.<sup>31-35</sup>

Dystonic tremor is a frequent clinical sign in dystonia<sup>36</sup> and tremor is a source of reduced QoL in other tremor types.<sup>37</sup> The impact of dystonic tremor on HR-QoL in dystonia patients has previously not been sufficiently addressed. We found that dystonic tremor was negatively associated with physical functioning and pain-related QoL. Although patients were evaluated as symptoms returned after BoNT treatment, a sustained improvement in patients with long-term BoNT therapy cannot be excluded. Therefore, investigations of

BoNT-naive patients may reveal even stronger associations. Our results implicate the importance of treating dystonic tremor to improve HR-QoL.

Population-based studies illustrate age- and sex-dependent prevalence of psychiatric conditions with a decrease in people > 50 years of age and women being more anxious.<sup>6-8</sup> Controlling our analysis for age and sex, HR-QoL in dystonia patients did not differ between men and women, while younger age in dystonia was associated with reduced emotional well-being and vitality.

The question of whether NMS are a primary phenomenon of the disease or a secondary response to physical impairment remains unanswered.<sup>15</sup> In dystonia as well as in Parkinson's disease the most potent predictors of HR-QoL appear to be depression and anxiety.<sup>38 39</sup> An increased risk of recurrent major depressive episodes in manifesting and non-manifesting *TOR1A* mutation carriers argues for a primary phenomenon,<sup>40</sup> while higher depression and anxiety scores in symptomatic but not in asymptomatic *SCGE* carriers may argue for this to be a secondary epiphenomenon with the limitation that in most *SCGE* carriers the mutated allele will be silenced.<sup>41</sup> Recent reports of familial coaggregation of psychiatric comorbidities in dystonia and an impaired theory of mind in cervical dystonia support shared genetic factors.<sup>42 43</sup> High prevalences of social anxiety in dystonia and QoL predictors as low self-esteem, self-deprecation, and educational level in cervical dystonia<sup>16</sup> point towards an impact of MS on HR-QoL although for most dystonias there may be a bidirectional and dynamic relationship between MS and NMS.<sup>15</sup>

Our study has certain limitations: The size of the cohort allows for drawing meaningful conclusions, even while controlling for important confounders, such as sex and age. Nevertheless further factors such as educational level, marital and socioeconomic status may significantly influence HR-QoL and were not assessed to guarantee statistical power.

A considerable proportion of patients were treated with oral anti-dystonic drugs and/or antidepressants. Their influence on NMS was not controlled for because the mechanism of action strongly varies across drug classes and some patients received medication from more than one drug class and with different dosages. Given the different drug targets and the contradictory or independent mechanisms (e.g. dopaminergics vs. anti-dopaminergics or anti-dystonic vs. anti-depressive effects) as well as the co-medication in several patients we refrained from a combined analysis. One of the inclusion criteria was disease duration less than five years, which prevented the assessment of later disease stages. Another limitation of our study is that only carriers of known mutations in dystonia-related genes were excluded but that no systematic screening was performed. Furthermore, new genes may not have yet been identified at the time point of the study, e.g. VPS16 which was very recently described in the context of dominantly inherited isolated dystonia.<sup>44</sup> The rationale to exclude patients with a monogenic background was to account for a potential confounder as they may present with a distinct neuropsychiatric profile and a different burden of NMS. The mutation frequency is, however, very low in isolated dystonia cases whereas the likelihood to identify causative mutations is considerably higher in combined or complex dystonias as previously shown in a large dystonia sample where exome sequencing was performed.<sup>45 46</sup> Further, mutations in dystonia-related genes are enriched in generalized or multifocal dystonia although it can be very rarely found in patients with focal dystonias. As most patients in our sample suffered from focal dystonia (62%) we thus assume that the number of unidentified mutations will be relatively low. The BFMDRS is a validated<sup>25</sup> and commonly used rating scale for dystonia but it may not be sensitive enough for focal dystonias. Furthermore, dystonic tremor is an important clinical feature that is not well reflected in currently used clinical scales. Accordingly, the qualitative assessment in this study (tremor

yes/no) is no longer appropriate to account for the specific features of dystonic tremor including distribution in different body regions, frequency, amplitude, regularity in frequency and amplitude, and alleviating or provoking maneuvers. Another pre-requisite is the sensitivity of a clinical rating scale to change, e.g. due to treatment. This is reflected by a recent paper showing that the diagnosis of dystonic tremor is still problematic because of different opinions on its very definition even across experts.<sup>47</sup>

HR-QoL in isolated dystonia is strongly associated especially with NMS as well as less related to MS, while standard therapy regimens only concentrate on the physical symptoms. Comprehensive care of dystonia patients should address both physical and mental health and aim to improve acceptance of the disease and coping strategies.

## TABLES

**Table 1**

HR-QoL and BFMDRS: Mean RAND 36-Item Health Survey total scores (range 0-100%) and mean BFMDRS scores with standard deviation of all patients and per type of dystonia.

Depression, GAD, SAD: Percentage and numbers of patients with symptoms of depression (HADS-D > 7), GAD (HADS-A > 7), SAD (LSAS > 30) and mean HADS-D, mean HADS-A and mean LSAS scores with standard deviation of all patients and per type of dystonia.

Tremor: Percentage and numbers of patients with dystonic tremor of all patients and per type of dystonia.

**Table 2**

Path analysis: Numerical estimates and 95% confidence intervals as indicators of the strength of the relationships between the eight HR-QoL subscales (RAND 36-Item Health Survey) and dystonia severity (BFMDRS), tremor, severity of depression (HADS-D), severity of **generalized** anxiety (HADS-A), severity of social anxiety (LSAS), age and sex in 603 dystonia patients. \*\* Bonferroni corrected  $\alpha \leq 0.006$ ; \*\*\* $p \leq .001$

## FIGURES

**Figure 1.** Simultaneously estimated bivariate correlations obtained from a saturated path analysis

Stylized illustration to demonstrate the strength of the relationships between the eight HR-QoL subscales (RAND 36-Item Health Survey) and dystonia severity (BFMDRS), tremor, severity of depression (HADS-D), severity of **generalized** anxiety (HADS-A), severity of social anxiety (LSAS) in 603 dystonia patients.

## **AUTHOR CONTRIBUTIONS:**

Johanna Junker, acquisition of data, study concept and design, analysis and interpretation of data, drafting of manuscript

Brian D. Berman, acquisition of data, critical revision of manuscript for intellectual content

James Hall, statistical analysis, critical revision of manuscript for intellectual content

Deena Wahba, acquisition of data, critical revision of manuscript for intellectual content

Valerie Brandt, statistical analysis, critical revision of manuscript for intellectual content

Joel S. Perlmutter, acquisition of data, critical revision of manuscript for intellectual content

Joseph Jankovic, acquisition of data, critical revision of manuscript for intellectual content

Irene A Malaty, acquisition of data, critical revision of manuscript for intellectual content

Aparna W. Shukla, acquisition of data, critical revision of manuscript for intellectual content

Stephen G. Reich, acquisition of data, critical revision of manuscript for intellectual content

Alberto J. Espay, acquisition of data, critical revision of manuscript for intellectual content

Kevin R. Duque, acquisition of data, critical revision of manuscript for intellectual content

Neepa Patel, acquisition of data, critical revision of manuscript for intellectual content

Emmanuel Roze, acquisition of data, critical revision of manuscript for intellectual content

Marie Vidailhet, acquisition of data, critical revision of manuscript for intellectual content

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

**Statistical Analysis** conducted by James Hall, DPhil, and Valerie Brandt, PhD, University of Southampton

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James Hall has no financial or non-financial disclosures to declare.

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Stephen G. Reich has active or recent grant support from NINDS and royalties from Springer and Informa. He has also served as a consultant for Best Doctors and as a reviewer for UpToDate. He serves on the Data Safety Monitoring Board for Enterin.

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