

**UNIVERSITY OF MEDICINE AND PHARMACY  
“CAROL DAVILA” BUCHAREST  
FACULTY OF MEDICINE**

**DOCTORAL THESIS**

**SUMMARY**

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**BUCHAREST**

**2023**

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**CLINICAL PROFILE, EVOLUTION AND IMPACT ON QUALITY  
OF LIFE IN IDIOPATHIC FOCAL DYSTONIA**

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2023

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## **1. The current state of knowledge**

### ***The importance of the topic***

A heterogeneous multitude of movement disorders is grouped under the general term dystonia. The clinical presence of dystonia ranges from an isolated presence of dystonia to its presence as a sign that occurs simultaneously in a multisystemic disease.

Dystonia is the third, most common, movement disorder after Parkinson's disease and essential tremor. However, in contrast to other degenerative neurological entities, dystonia has, despite scientific advances, limited therapeutic approaches.

We can certainly say that dystonia is a debilitating and disfigured disorder that affects many aspects of patients' daily lives; thus, severe muscle contractions that characterize the disease can interfere with basic daily functions such as walking, sitting, eating, and speaking. Through uncomfortable postures, patients with dystonia show a disfigured appearance, which is associated with embarrassment and embarrassment leading to social isolation.

Taking all this into account, the quality of life assessment must be increasingly recognized as important in the diagnosis and management of patients with dystonia.

Choosing a neurology theme such as dystonia with a focus on an important aspect such as the quality of life of patients is topical for both research and clinical practice and represents an important motivation in choosing the theme of the doctoral thesis.

### ***The motivation for choosing the research topic***

The World Health Organization (who) defines quality of life as a broad concept that incorporates into a complex system physical health, psychological state, level of independence, social relations and personal expectations of the patient with the basic characteristics of the environment in which the patient lives.

Quality of life is a complex, holistic and personal concept that cannot be easily measured. Thus, we can say that there is no direct relationship between disease, disability and a poor quality of life, but rather a perception of the patient that changes as his health deteriorates.

The concept of quality of life is associated with all conditions, whether neurological or not. In the case of the patient diagnosed with dystonia – chronic, disabling condition and limited therapeutic resources, the quality of life must be a major criterion, along with the clinical manifestation, to guide the management plan.

Thus, the doctoral thesis aims to study the quality of life of the patient diagnosed with dystonia and the factors that influence it, so as to provide useful tools for a multimodal approach to therapy. Although there are clinical studies and series of cases in the literature that concern themselves with addressing certain isolated types of dystonia – such as blepharospasm and torticollis – the doctoral thesis extensively evaluates patients with different forms of dystonia.

## **2. The research hypothesis**

The purpose of the paper is to assess the quality of life in a group of patients with a certain diagnosis of dystonia in order to identify the main factors contributing to its alteration. Knowing these factors would make it possible to approach them simultaneously with the specific treatment of dystonia, customizing the treatment and increasing its success.

The doctoral thesis consists of two clinical studies that analyzed 221 patients diagnosed with dystonia at the Neurology Clinic of the Colentina Clinical Hospital, Bucharest, Romania. The positive diagnosis was established by the specialist neurologist based on clinical and paraclinical elements, management being differentiated based on individual particularities.

For the analysis of non-motor manifestations, questionnaires and internationally validated scales were used, as well as a questionnaire made to collect data on the impact of the COVID-19 pandemic on the Romanian patient with dystonia.

The statistical analysis was carried out with the IBM SPSS program version 23.0 for Windows. The statistical tests used are the square Chi test (including Fisher variant), the student test. Calculated estimates are accompanied by 95% confidence intervals (95% CI) to be able to compare results in sub-analyses. and all tests were considered significant if  $p < 0.05$ .

In order to deepen the quality of life in the Romanian patient with dystonia, the doctoral thesis includes 2 studies conducted by the doctoral student on neurological casuistics and which aim to have well defined objectives:

**Study 1:** Non-motor manifestations and quality of life in patients with idiopathic dystonia with focal onset performed on 131 patients with a definite diagnosis of dystonia and where the quality of life was evaluated by using internationally validated questionnaires for calculating scores that assess quality of life dependent on health short form 36 Health A study (SF-36), the cognitive function Montreal cognitive Assembly (MoCA), and the depression patient Health questionnaire-9 (PHQ-9).

**Study 2:** The quality of life and the impact of the COVID-19 pandemic on patients with dystonia made on 90 patients where, besides the quality of life that was evaluated by EuroQol-5 dimension (EQ-5D), a questionnaire with 44 questions was also applied, which tried to assess the impact of the COVID-19 pandemic on the Romanian patient with dystonia.

### **3. Materials and methods**

The doctoral thesis consists of 2 studies conducted by the doctoral student on neurological casuistics and which aim at well-defined objectives.

**Study 1.** Non-motor manifestations and quality of life in patients with idiopathic dystonia with focal onset

The study conducted in this part of the doctoral thesis was transversal, descriptive type performed on a total of 131 patients diagnosed by the neurologist. All patients addressed the neurology service of the Neurology Clinic of Colentina Clinical Hospital, Bucharest, which is a specialized tertiary center and probably one of the largest delivery centers for Botulinum toxin injection services for patients with movement disorders between November 2017 and January 2020.

Both inclusion and exclusion criteria were used in the study.

*Inclusion criteria:*

1. Idiopathic dystonia with focal isolated onset (diagnosed by the neurologist according to MDS criteria) in adulthood, with or without progression

2.ethnic Romanian

*Exclusion criteria:*

1. generalized and multifocal dystonia, segmentation at onset
2. Secondary dystonia
3. Primary dystonia with definite Mendelian transmission
4. Known genetic mutations - the main causes of the appearance of dystonia
5. Comorbidities that interfered with the evaluation

The variables are of discrete and continuous quantitative type with the recording of variants and values in the database necessary for defining the dystonia. The data were correlated and analyzed anonymously including the following variables for the whole lot:

- age at onset of dystonia
- current age at referral to a neurologist
- sex
- environment of origin
- education
- type of occupation
- comorbidities (cardiovascular, muscle disease, other neuro-degenerative diseases, movement disorders, trauma)
- hereditary history (cardiovascular diseases, neurological diseases, motion diseases, dystonia, others)
- alcohol/smoking behavior before diagnosis of dystonia and after
- possible exposure to toxic substances – the environment in which they work
- characteristics of dystonia
  - a location of dystonia at onset
  - the current location
  - an affected anatomical area
  - a pattern of temporal evolution
  - an association with changes in imaging
- Quality of life assessment using questionnaires used to calculate scores that assess health-dependent quality of life (SF36), cognitive function (MoCA) and depression (PHQ-9).

**Study 2.** Quality of life and the impact of the COVID-19 pandemic on patients with dystonia

In this part of the doctoral thesis, I conducted a descriptive, transversal study that took place between May and September 2021. The study ensured patient anonymity and data protection. The study was approved by the local Research Ethics Commission.

The following inclusion criteria have been applied:

- over 18 years of age;
- romanian speakers;
- a definite diagnosis of dystonia or hemifacial spasm, regardless of the type of dystonia or the duration of treatment prior to the start of the study
- informed consent given in writing by the patient or a legal representative
- the absence of any disability that could affect the self-administration of study questionnaires during hospital visits (for example, bilateral blepharospasm that affects the vision or invalidation of hand postures that render handwriting impossible to practice).

Demographic and clinical variables were selected with numeric records and response variants.

The variables are of discrete and continuous quantitative type with the recording of variants and values in the database necessary for defining the dystonia. The data were correlated and analyzed anonymously including the following variables for the whole lot:

- age at onset of dystonia
- current age at referral to a neurologist
- duration of the disease
- comorbidities (cardiovascular, ophthalmological, psychiatric, rheumatological, neurological, Gastroenterological, gynecological, diabetes mellitus, allergy, ENT, endocrinological, pulmonary)
- relevant hereditary history
- distribution of dystonia
- the type of dystonia

Two separate questionnaire sets were administered during the study period: A validated, more quantitative questionnaire on the quality of life of the patient in general (EQ-5D) and a more qualitative questionnaire designed by the research team on pandemic-related specificity, but not validated to date.



The EuroQol-5 dimension questionnaire (EQ-5D) is a quality of life questionnaire consisting of 5 areas as follows: mobility, self-care, regular activities, pain/discomfort and anxiety/depression plus an analog thermometer scale defined between 0 and 100 waves of 0 (worst-felt health) and 100 (best-felt health).

The survey conducted by the research team consisted of 2 subgroups: General data related to demographic information, diagnosis of dystonia, presence of comorbidities and specific data where there were 3 subgroups as follows: Access to treatment (consisting of 13 questions WITH YES/NO), worsening manifestations / interference with social restrictions (made up of 12 QUESTIONS WITH YES/NO) and vaccination (made up of 10 QUESTIONS WITH YES/NO).

Quantitative variables testing was performed with descriptive statistical techniques. Continuous quantitative variables are reported with mean, and standard deviation dispersion, amplitude measured by observing the minimum and maximum value in the range of values. Frequencies and proportions were calculated. The statistical analysis was carried out with the IBM SPSS program version 23.0 for Windows. The statistical tests used are the square Chi test (including Fisher variant), the student test, the alpha Cronbach coefficient, the Spearman coefficients. Calculated estimates are accompanied by 95% confidence intervals (95% CI) to be able to compare results in sub-analyzes.

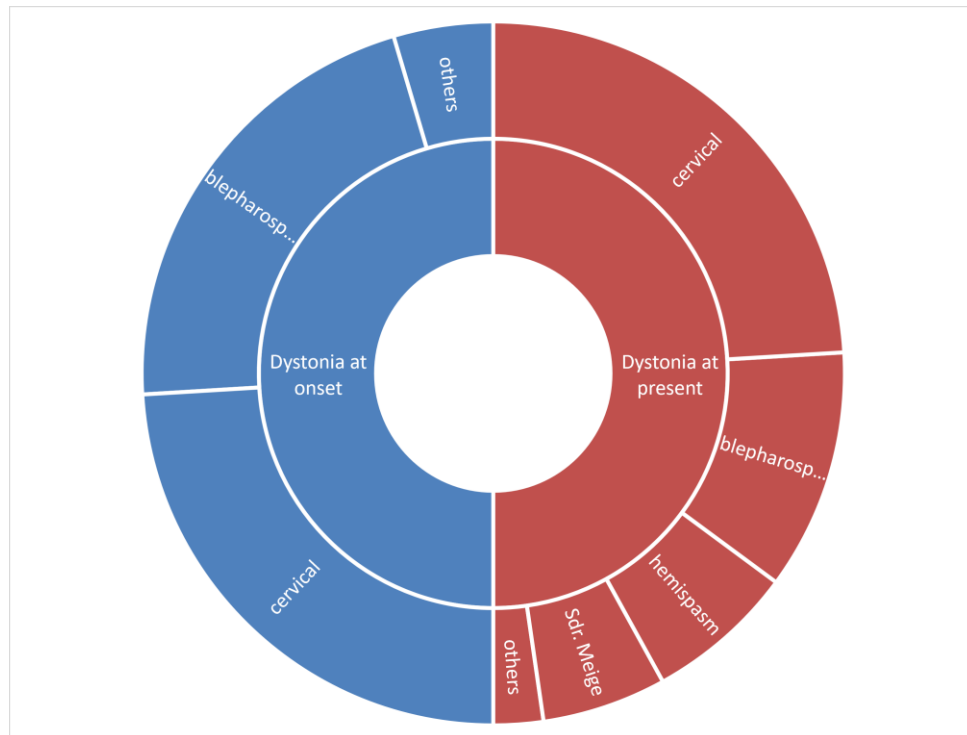
#### **4. Results and discussion**

The study group totaled a total of 131 patients with an average age of 54.09 years, the youngest patient was 20 years and the oldest 82 years, with a large age dispersion of the patients included in the study (standard deviation = 14 years).

The average age of patients in the study group at the time of onset of dystonia was 45 years (standard deviation of +/-13 years), the minimum age at onset was 18 years and the maximum age was 74 years.

	Frequency	Percent	Valid Percent	Cumulative Percent
<24	2	1.5	1.5	1.5
25-34	12	9.2	9.2	10.7
35-44	21	16.0	16.0	26.7
45-54	29	22.1	22.1	48.9
55-64	34	26.0	26.0	74.8
>=65	33	25.2	25.2	100.0
<b>Total</b>	131	100.0	100.0	

Based on patient data, we identified a subgroup of patients who transition from focal dystonia to segmental or multifocal dystonia through clinical overflow or progression of dystonia.



Evolution of dystonia type from onset to present (N=131)

Of the total 131 patients we had 65 patients who were analyzed for non-motor manifestations. They were divided according to the temporal pattern into patients with stationary evolution (remain with focal manifestations) – 45 (70%) patients and with progressing to the progressive form – 20 (30%) patients.

Regarding the B/F ratio, this is 1/2 on the entire study group (n=131), but becomes 1/4 in the subplot of patients who answered the evaluation questionnaires.

Of the total 131 patients, 65 (49.61%) patients with dystonia who have completed the evaluation tools for the following non-motor elements for defining quality of life: Neurocognitive disorder (MoCA score), depressive disorder (PHQ-9) and quality of life (SF-36).

Thus, the cognitive status was assessed by using the MoCA test. Of the 65 patients evaluated, the vast majority, almost two-thirds 42 (64.62%) patients do not have cognitive impairment according to the MoCA test, while 22 (33.85) patients had mild cognitive impairment and only 1 patients had moderate cognitive impairment.

At the time of the study, we notice that the average MoCA score is lower in progressive forms, with an average of 25.25 points (n=20 patients), Below the 26 points threshold for the MoCA test, compared to stationary forms, where the average score is 26.75 points (n=45 patients), higher than the threshold set for the MoCA (>26 points). The difference of 1.5 points in the average score between stationary and progressive forms is statistically insignificant (CI95% with values of -3,114 to 0,114, p=0,068).

Distribution of neurocognitive impairment according to the form of dsitonia (N=65)

<b>Type of dystonia</b>	<b>N</b>	<b>%</b>	<b>Mean score MoCA (points)</b>	<b>Standard deviation</b>	<b>CI 95 % and p</b>
<b>stationary</b>	45	69.2	26.75	2.8	-3.114 la 0.114 p = 0.068
<b>progressive</b>	20	30.8	25.25	3.2	
<b>Total</b>	65	100			

Of the 45 stationary patients, there were 11 men and 34 women, and there is no statistically significant difference in the MCA score between men and women in this subgroup of patients (BUT 95% with values of -0,507 to 2,871 p=0,162).

Distribution of neurocognitive impairment by gender in patients with stationary dystonia  
(N=45)

<b>Gender</b>	<b>N</b>	<b>%</b>	<b>PHQ-9 mean score (points)</b>	<b>Standard deviation</b>	<b>CI95% and p</b>
<b>male</b>	11	24.4	27.64	2.06	-0.507 la 2.871 p =0.162
<b>female</b>	34	75.6	26.45	3.08	
<b>Total</b>	45	100			

Of the 20 patients with progressive dystonia, there were 18 women and only 2 men. Gender MoCA score analysis in this type of patients shows a lower average score in women (25.06 points) than in men (27.00 points), statistically significant but very high dispersion difference (CI 95% -0,278 in 3,611, p=0,025).

Distribution of neurocognitive impairment by gender in patients with progressive dystonia  
(N=20)

<b>Gender</b>	<b>N</b>	<b>%</b>	<b>PHQ-9 mean score (points)</b>	<b>Standard deviation</b>	<b>CI95% and p</b>
<b>male</b>	2	10	27.00	0	-0.278 la 3.611 p=0.025
<b>female</b>	18	90	25.06	3,35	
<b>Total</b>	20	100			

The PHQ-9 scale was used to evaluate depression. And this test was applied to 65 of the 131 patients who made up the study group. Thus, 35 (53.85%) of those tested do not experience depression, 15 (23.08%) patients have mild depression, 8 (12.31%) patients have moderate depression, 4 (6.15%) patients have moderate-severe depression, and only 3 (4.62%) patients have severe depression.

The average PHQ-9 score is higher among patients with stationary dystonia, i.e. 5.6 points, while among patients with progressive dystonia the average score of PHQ-9 is 6.75 points, but this difference of 1.11 points is statistically insignificant (CI95% with values of -2,311 to 4,538, p=0,518).

Distribution of neurocognitive impairment according to the form of dsitonia (N=65)

<b>Gender</b>	<b>N</b>	<b>%</b>	<b>PHQ-9 mean score (points)</b>	<b>Standard deviation</b>	<b>CI95% and p</b>
<b>male</b>	13	20	5.46	8.48	-5.910 la 4.680 p=0.808
<b>female</b>	52	80	6.08	5.69	
<b>Total</b>	65	100			

There are differences between the two genders in terms of depression in the study group (n=65). Of the 65 patients tested with the PHQ-9 scale, 13 are male and 52 are female. The average PHQ-9 score in women was 6.08 points and in men was 5.46 points, but the confidence interval is wide and the differences between genders are statistically insignificant (CI95% with values of -5,910 to 4,680, p=0,808).

Distribution of depression by gender in patients with stationary and progressive dystonia (N=65)

<b>Gender</b>	<b>N</b>	<b>%</b>	<b>PHQ-9 mean score (points)</b>	<b>Standard deviation</b>	<b>CI95% and p</b>
<b>male</b>	13	20	5.46	8.48	-5.910 la 4.680 p=0.808
<b>female</b>	52	80	6.08	5.69	
<b>Total</b>	65	100			

As with the MoCA score, there are no significant differences between men and women in both stationary and progressive dystonia patients (CI95% with -5.407 to 4.195, p=0.836).

Distribution of depression by gender in patients with stationary dystonia (N=45)

<b>Gender</b>	<b>N</b>	<b>%</b>	<b>PHQ-9 mean score (points)</b>	<b>Standard deviation</b>	<b>CI95% and p</b>
<b>male</b>	11	24.4	5.18	8.86	-5.407 la 4.195 p=0.836
<b>female</b>	34	75.6	5.79	6.06	
<b>Total</b>	45	100			

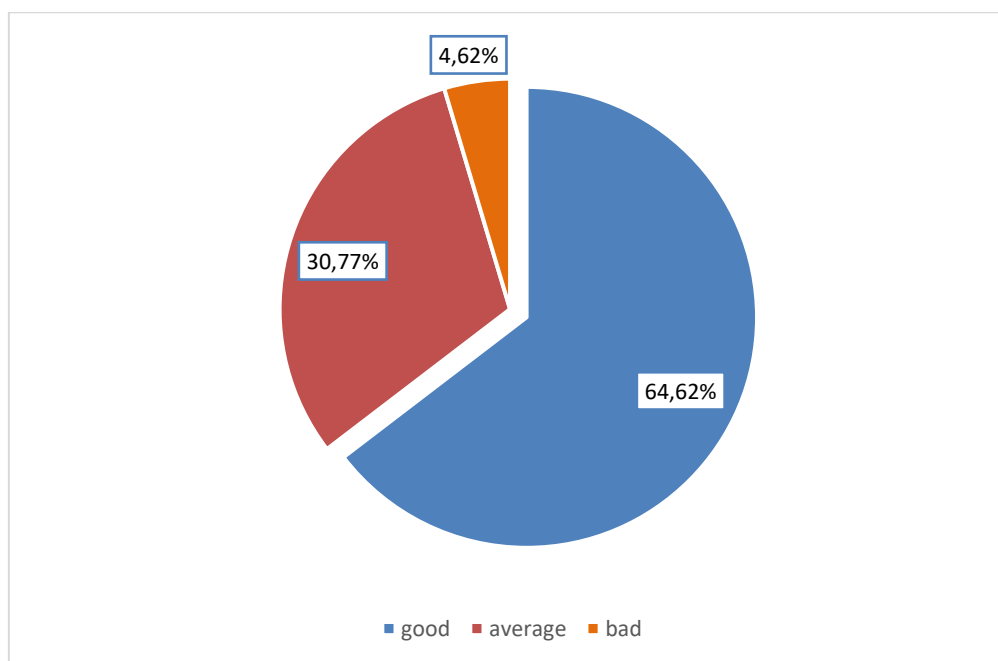
Of the 20 patients with progressive dystonia, 18 are women and only 2 are men. The analysis of the PHQ-9 score by gender in this type of patients shows an average score in women lower 6.72 points than that of men 7.00 points, statistically insignificant but with very low dispersion (CI 95 % -8.280 in 8.836, p=0.971).

Distribution of depression by gender in patients with progressive dystonia (N=20)

Gender	N	%	PHQ-9 mean score (points)	Standard deviation	CI95% and p
male	2	10	7.00	8.48	-8.280 la 8.836 p=0.971
female	18	90	6.72	5.23	
<b>Total</b>	20	100			

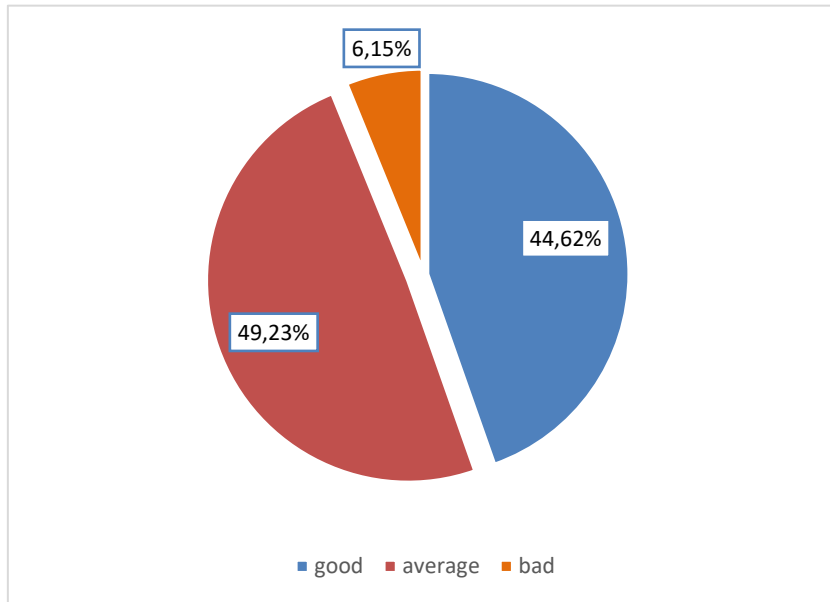
The distribution of observations generally shows statistically insignificant differences in the MOCA and/or PHQ-9 scores by gender and/or form of evolution of stationary versus progressive dystonia, a single statistical difference in the form of progressive evolution in the case of the MoCA score.

The quality of life was assessed using the SF-36 questionnaire for both physical and mental health. Of the 65 patients tested, the vast majority of 42 (64.62%) had good physical health, 20 (30.77%) had average physical health, and only 3 (4.62%) had poor physical health.



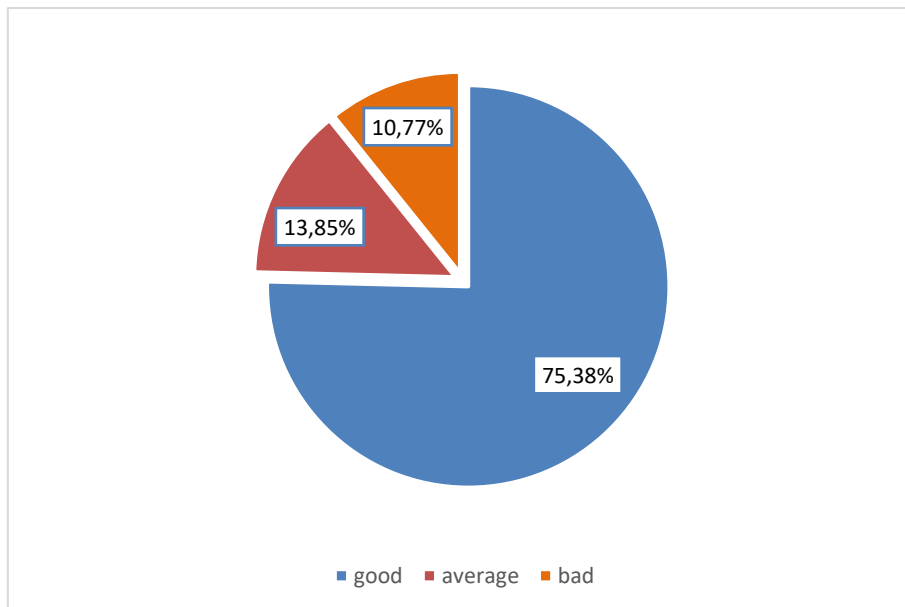
Group structure by physical health score rated on SF-36 scale (N=65)

Regarding the second part of the SF-36 mental health questionnaire, we note that the vast majority of those surveyed, i.e. 32 (49.23%) patients had average mental health, 29 (44.62%) patients had good mental health and only 4 (6.15%) patients had poor mental health.



Group structure by mental health score rated on SF-36 scale (N=65)

After calculating the SF-36 overall health score, the vast majority of patients among the 65 interviewed, 49 (75.38%) patients are in good overall condition, 9 (13.85%) patients are in average overall condition and 7 (10.77%) are in poor overall condition.



Group structure by overall health score (total score SF-36) (N=65)



Regardless of the form of evolution of the disease (stationary/progressive) on the group of 65 patients we notice an important impairment of quality of life through SF36 in the following areas: Role limitation due to physical problems (mean value 51.27 points), somatic pain (mean value 58.19 points) and energy/vitality (mean value 58.69 points). Other areas of SF36 such as social function (mean value 84.29 points), physical function (mean value 73.85 points) and emotional cause role limitation (mean value 77.44 points) showed higher scores that we can attribute to the fact that tests were performed after botulinum toxin injection.

The average scores of SF-36 throughout the study group (n=65) regardless of the form of evolution of the dystonia

<b>Subscore SF-36</b>	<b>N</b>	<b>Min</b>	<b>Max</b>	<b>Mean</b>	<b>Standard deviation</b>
<b>SF-36 PF (physical functioning)</b>	65	0	100	<b>73.85</b>	24.1
<b>SF-36 RP role physical</b>	65	0	100	<i>51.27</i>	45.1
<b>SF-36 BP (bodily pain)</b>	65	0	100	<i>58.19</i>	32.5
<b>SF-36 GH (general health)</b>	65	20	100	61.48	25.3
<b>SF-36 VT (vitality)</b>	65	0	95	<i>58.69</i>	23.7
<b>SF-36 SF (social functioning)</b>	65	0	100	<b>84.29</b>	29.3
<b>SF-36 RE (role emotional)</b>	65	0	100	<b>77.44</b>	40.4
<b>SF-36 SM (mental health)</b>	65	12	96	64.18	20.6

We further analyzed the group of 65 patients depending on the type of stationary or progressive dystonia. Thus, the 45 stationary patients had more affected areas in SF-36 such as: Role limitation due to physical problems (mean value 60.4 points), somatic pain (mean value 61.7 points) and energy/vitality (mean value 62.0 points). Areas that had higher values for SF-36 in patients with stationary dystonia were: Social function (mean value 83.4 points), emotional cause role limitation (mean value 80.7 points) and physical function (mean value 77.8 points).

Average SF-36 scores in patients with stationary dystonia (N=45)

<b>Subscore SF-36</b>	<b>N</b>	<b>Min</b>	<b>Max</b>	<b>Mean</b>	<b>Standard deviation</b>
<b>SF-36 PF (physical functioning)</b>	45	0	100	<b>77,8</b>	21.8
<b>SF-36 RP role physical</b>	45	0	100	60,4	42.2
<b>SF-36 BP (bodily pain)</b>	45	0	100	61,7	31
<b>SF-36 GH (general health)</b>	45	25	100	65,7	25.5
<b>SF-36 VT (vitality)</b>	45	0	95	62,0	22.3
<b>SF-36 SF (social functioning)</b>	45	0	100	<b>83,4</b>	30
<b>SF-36 RE (role emotional)</b>	45	0	100	<b>80,7</b>	37.2
<b>SF-36 SM (mental health)</b>	45	12	96	67	20.6

For the 20 patients with progressive form had more affected areas in SF-36 such as: Role limitation due to physical problems (mean value 32.24 points), energy / vitality (mean value 50.79 points) and general health perception (mean value 51.32 points). Areas that had higher

values for SF-36 in patients with progressive dystonia were: Social function (mean value 85.83 points), emotional-cause role limitation (mean value 62.42 points) and physical function (mean value 63.68 points).

Average scores of SF-36 in patients with progressive dystonia (N=20)

<b>Subscore SF-36</b>	<b>N</b>	<b>Min</b>	<b>Max</b>	<b>Mean</b>	<b>Standard deviation</b>
<b>SF-36 PF (physical functioning)</b>	20	25	100	<b>63,68</b>	27.1
<b>SF-36 RP role physical</b>	20	0	100	32,24	46.2
<b>SF-36 BP (bodily pain)</b>	20	0	100	51,45	35.5
<b>SF-36 GH (general health)</b>	20	20	95	51,32	23
<b>SF-36 VT (vitality)</b>	20	0	85	50.79	26.2
<b>SF-36 SF (social functioning)</b>	20	13	100	<b>85.83</b>	28.6
<b>SF-36 RE (role emotional)</b>	20	0	100	<b>68.42</b>	47.7
<b>SF-36 SM (mental health)</b>	20	24	96	58.32	20.2

We also turned our attention to the fact that in the total group of 131 patients found 2 types of predominant focal dystonia, namely cervical dystonia and blepharospasm, in the desire to compare the differences between the two types of dystonia.

Of the 131 patients, 63 patients were diagnosed with cervical dystonia, having at the onset of the disease an average age of 42.31 years (minimum 19 years, maximum 72 years with a standard deviation of 12.935), with an average age at the introduction of the study of 49.83

years (minimum 20 years, maximum 82 years with a standard deviation of 13.845) on average a duration of the disease of about 7 years.

We also analyzed non-motor manifestations (MoCA, PHQ-9, SF-36). Thus, we focused our attention on a number of 28 patients who had the average score of 26.46 points (minimum 18 points, maximum 30 points with a standard deviation of 3.426). For depression assessment, the average PHQ-9 score showed an average of 4.39 points (minimum 0 points, maximum 30 points with a standard deviation of 6.528).

For SF-36 we notice the following results regarding the physical state components: Average value of SF-36 FF-physical function of 79.29 points (minimum 35 points, maximum 100 points with a standard deviation of 20.033), average value of SF-36 RF - role limitation due to physical problems of 64.29 points (minimum 0 points, Maximum 100 points with a standard deviation of 42.725), mean value of SF-36 DS – somatic pain of 55.71 points (minimum 0 points, maximum 100 points with a standard deviation of 27.838) and mean value of SF36 SG – general health perception of 62.86 points (minimum 25 points, Maximum 100 points with a standard deviation of 20.880), while in the mental state components we find: Average value of SF36 VT - energy / vitality of 66.43 points (minimum 20 points, maximum 95 points with a standard deviation of 19.238), Mean value of SF36 FS - Social function of 87.95 points (minimum 0 points, maximum 100 points with a standard deviation of 24.880), mean value of SF36 RE-limit the emotional cause role of 80.95 points (minimum 0 points, maximum 100 points with a standard deviation of 36.772), Mean value of SF36 SM - mental health of 71.86 points (minimum 40 points, maximum 95 points with a standard deviation of 17.367).

Comparison of mean values for non-motor manifestations (cervical dystonia vs. blepharospasm)

	<b>Cervical dystonia (n=28)</b>		<b>Blepharospasm (n=17)</b>	
	Mean	Std.Deviation	Mean	Std.Deviation
<b>MoCA</b>	26,46	3,426	26,35	2,178
<b>PHQ-9</b>	4,39	6,528	7,71	7,016
<b>SF-36 PF (physical functioning)</b>	79,29	20,033	68,82	27,530

<b>SF-36 RP role physical</b>	64,29	42,725	42,35	44,128
<b>SF-36 BP (bodily pain)</b>	55,71	27,838	59,12	34,775
<b>SF-36 GH (general health)</b>	62,86	20,880	66,18	33,844
<b>SF-36 VT (vitality)</b>	66,43	19,238	51,47	24,734
<b>SF-36 SF (social functioning)</b>	87,95	24,880	73,77	36,347
<b>SF-36 RE (role emotional)</b>	80,95	36,772	76,47	43,724
<b>SF-36 SM (mental health)</b>	71,86	17,367	61,18	22,924

In the second studio the group included 90 patients, 22 men and 68 women, the average age was 58 years (standard deviation  $\pm 12.5$ ; range 21-82).

Of the 90 patients, the vast majority of 68 (75.56%) patients had onset of dystonia in adulthood (> 40 years), while 20 (22.22%) patients had onset in adulthood (21-40 years) and only one patient had onset in adolescence (13-20 years), respectively childhood (from birth to 2 years).

<b>Characteristic</b>	<b>Dystonia (n=72)<sup>1</sup></b>	<b>Hemifacial spasm (n=18)<sup>1</sup></b>	<b>p-value<sup>2</sup></b>
<b>Sex</b>	54/72 (75%)	14/18 (78%)	>0.9
<b>Age</b>	57.12 (12.65)	65.11 (10.15)	0.013
<b>Onset</b>	47.25 (12.37)	54.78 (9.29)	0.020
<b>Disease duration</b>	9.78 (7.67)	10.17 (8.23)	0.8
<b>Toxin Type</b>	50/72 (69%)	6/18 (33%)	0.005
<b>Treatment duration</b>	5.05 (4.00)	5.44 (4.03)	0.6
<b>Periodicity</b>			0.004
<b>3 months</b>	41/72 (57%)	3/18 (17%)	
<b>3-6 months</b>	22/72 (31%)	12/18 (67%)	
<b>6-12 months</b>	7/72 (9.7%)	2/18 (11%)	
<b>&gt;12 months</b>	0/72 (0%)	1/18 (5.6%)	
<b>NA</b>	2/72 (2.8%)	0/18 (0%)	

<sup>1</sup>n/N (%); medie (DS)

<sup>2</sup>Fisher's exact test; Wilcoxon rank sum test; Pearson's Chi-squared test

As can be seen from the data in Figure 4.3.13, approximately 2/3 (74%) of the patients in the batch were unable to access the attending physician for the periodic injection of botulinum toxin treatment.

Only 13 (15%) patients were able to get their treatment with injectable botulinum toxin in another hospital. For 10 (11%) of the 90 patients we do not have data.

As regards pandemic-related prevention measures, the vast majority of participants reported that they had no problems complying with hand hygiene regulations or wearing masks. Approximately 31 (34%) patients showed difficulty performing their usual sensory tricks, according to the summary data in Table 4.3.3. However, it should be stressed that all Hemifacial spasm patients included as did not provide data on sensory tricks, since Hemifacial spasm is not considered a dystonia in itself, And only 6 patients became infected with SARS-CoV-2 during the pandemic and 3 participants chose not to respond.

Given the restrictive measures that were applied during COVID-19, treatment of patients with dystonia and hemifacial spasm was postponed by an average of 8.5 months (SD±4.5, range 0-24) in the facility where patients were included. During the restrictive period of the pandemic, most participants would have considered that they were able to continue their usual treatment (94%); also, up to 80% had no access to a different clinic or could not afford to administer the injections. Only 19% opted for alternative treatments such as acupuncture. However, not all patients felt that their right to treatment was violated during the pandemic (61% - violation vs. 31% without violation).

For our patients, the EQ-5D scale was used for quality of life assessment. The average values of the 5 sub-ranges of the scale ranged from 1.73 (self-care) to 2.72 (pain).

Average values of sub-domains EQ-5D (N=90)

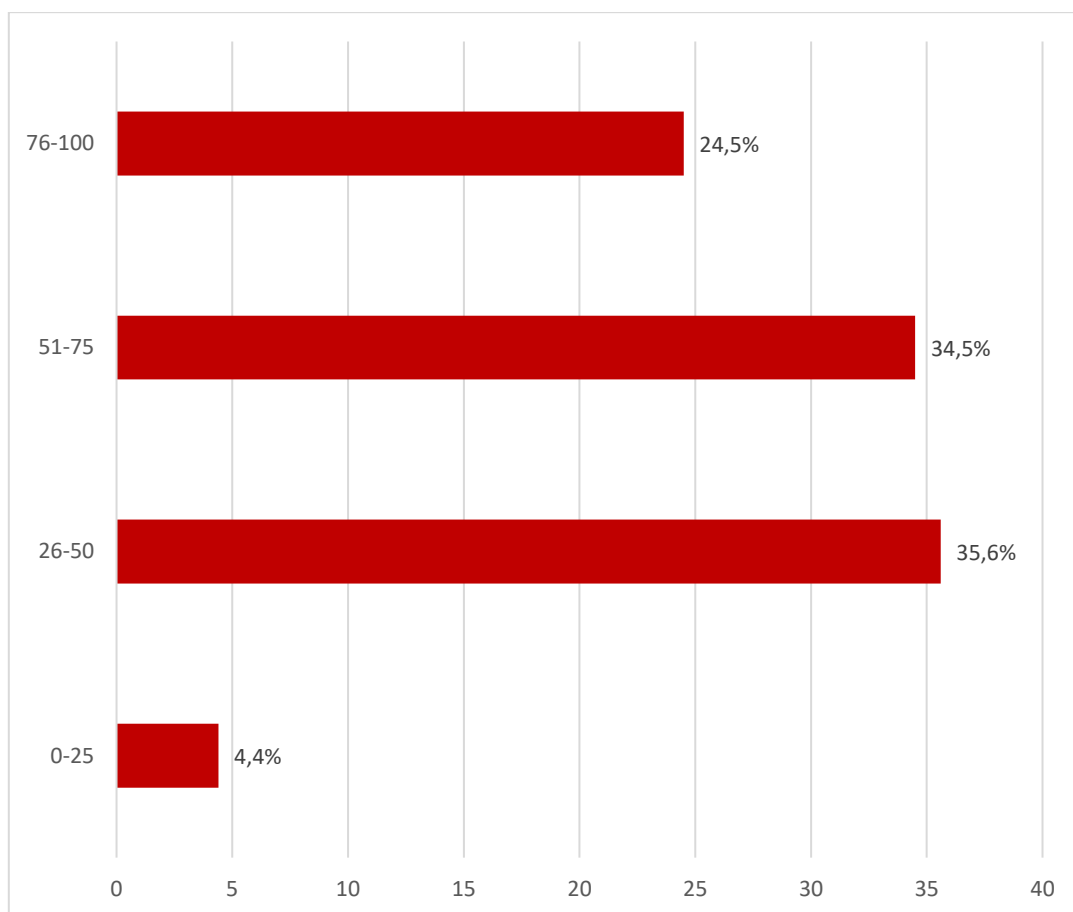
<b>EQ-5D</b>	<b>Mean</b>	<b>Median</b>	<b>Standard deviation</b>
<b>Mobility</b>	2,19	2,0	1,271
<b>Self-Care</b>	1,73	1,0	1,197
<b>Usual activities</b>	2,23	2,0	1,171
<b>Pain/Discomfort</b>	2,72	3,0	1,161
<b>Anxiety/depression</b>	2,17	2,0	1,144

Thus, for a better overview of the assessment offered for EQ-5D, the vast majority of potentially problematic variables were evaluated in the problem-free range – moderate problems, where mobility and self-care were largely categorized as problem-free, regular activities and anxiety/depression are problem-free to slightly problematic, and the pain in the vast majority of cases is moderately problematic.

EQ-5D distribution by severity (N=90)

	<b>Mobility N(%)</b>	<b>Self- Care N(%)</b>	<b>Usual activities N(%)</b>	<b>Pain/Discomfort N(%)</b>	<b>Anxiety/depression N(%)</b>
<b>Level 1 (no problems)</b>	37 (41)	59 (65)	30 (33)	16 (18)	32 (35)
<b>Level 2 (slight)</b>	22 (25)	11 (12)	27 (30)	21 (23)	26 (29)
<b>Level 3 (moderate)</b>	13 (14)	10 (11)	20 (22)	32 (35)	22 (24)
<b>Level 4 (severe)</b>	13 (14)	5 (6)	8 (9)	14 (16)	5 (6)
<b>Level 5 (extreme)</b>	5 (6)	5 (6)	5 (6)	7 (8)	5 (6)
<b>TOTAL</b>	90 (100)	90 (100)	90 (100)	90 (100)	90 (100)

The impact of dystonia on the general condition of patients with dystonia is self-assessed by the patient on THE VAS EQ scale as between 0 and 25 for 4 (4%) patients, between 26 and 50 for 32 (36%) patients, between 51 and 75 for 31 (35%) patients and between 76 and 100 for 22 (25%) patients.



The impact of dystonia on the EQ VAS scale (n=90)

The Spearman correlation coefficient was calculated to assess the relationships between the EQ-5D scale domains. The results showed that there is a statistically significant positive correlation between all five areas (mobility, self-care, activity, pain, anxiety). The highest correlation is between mobility and activity,  $r(88) = .71, p < .01$ , and the lowest correlation is between self-care and anxiety,  $r(88) = .37, p < .01$ .



Correlation coefficient Spearman's Rho. Correlations between the EQ-5D domains  
(N=90)

	<b>Mobility</b>	<b>Self-Care</b>	<b>Usual activities</b>	<b>Pain/Discomfort</b>	<b>Anxiety/depression</b>
<b>Mobility</b>	1,000				
<b>Self-Care</b>	,627	1,000			
<b>Usual activities</b>	,712	,587	1,000		
<b>Pain/Discomfort</b>	,536	,476	,608	1,000	
<b>Anxiety/depression</b>	,442	,369	,538	,612	1,000

## 5. Conclusions

1. Doctoral thesis Clinical profile, evolution and impact on quality of life in idiopathic focal dystonia had as main objective the analysis of quality of life and non-motor elements of patients with dystonia in Romania.

2. Assessment of non-motor phenomena and quality of life using the SF-36 questionnaire was performed on 65 patients who agreed to be investigated out of a total of 131 patients.

3. The evaluation of the quality of life using the EQ-5D scale and the impact of the COVID-19 pandemic was carried out on a batch of 90 patients.

4. patients with progressive dystonia had more significant neurocognitive impairment than patients with stationary dystonia (mean MoCA score 25.25 points vs. 26.75 points).

5. Of patients with progressive dystonia when assessing the presence of neurocognitive disorder compared to women and men, we notice the presence of neurocognitive impairment in women while in men this is absent (average MoCA score 25.06 points vs. 27.0 points)

6. The vast majority of patients do not experience depression (53.85%), but for those with depressive manifestations, patients with progressive dystonia scored worse than those with

stationary dystonia (average score PHQ-9 6.75 points-progressive, respectively 5.6 points-stationary).

7. Both for the entire study group and for patients with stationary dystonia, women had a lower PHQ-9 score (mean PHQ-9 5.46 points – total male, respectively 6.08 points – total female and average PHQ-9 5.18 points – stationary male, Respectively 6.08 points – female stationary), but in the analysis of progressive patients, the male gender had more depressive manifestations, (average score PHQ-9 7.00 – male progressive, respectively 6.78 – female progressive).

8. When analyzing the quality of life through the SF-36 questionnaire on the entire analyzed lot, but also separately in stationary and progressive dystonia, he showed that the most affected areas were in all three cases the role limitation due to physical problems (average value 51.27 points vs 60.4 points vs 32.4 points), energy / vitality (mean value 58.69 points vs 62 points vs 50.79 points), while for the entire analyzed lot and stationary dystonia the area between the most affected was somatic pain (mean value 58.19 points vs 51.6 points), and for progressive dystonia was the perception of general health (mean value 51.32 points).

9. Comparative analysis of non-motor and quality of life manifestations between patients with blepharospasm and cervical dystonia showed that from the point of view of neurocognitive impairment by the MoCA score there are no significant differences (26.46 points vs. 26.35 points – without present neurocognitive disorder), And in terms of depressive manifestations quantified by the PHQ-9 questionnaire, a higher score is noted that corresponds to the presence of mild depression only in the case of blepharospasm (7.71 points), while in the case of cervical dystonia the presence of depression is not observed (4.39 points).

10. Compared with cervical dystonia and blepharospasm in terms of quality of life assessment through SF-36 we have in case of cervical dystonia the most affected areas were: somatic pain (55.71 points), general health perception (62.86 points) and role limitation due to physical problems (64.29 points), and the areas least affected were: social function (87.95 points), limitation of the role of emotional cause (80.95 points) and physical function (79.29 points), while in the case of blepharospasm the most affected areas were: the role limitation due to physical problems (42.35 points), energy/vitality (51.47 points) and somatic pain (59.12 points), and the areas least affected were: limitation of the role of emotional cause (76.47 points), social function (73.77 points) and physical function (68.82 points).

11. In connection with the impact of the COVID-19 pandemic, only 2/3 (74%) of patients were unable to access the attending physician for the periodic injection of botulinum toxin treatment and only 13 (15%) patients were able to get to administer their injectable botulinum toxin treatment in another hospital.

12. Compliance with hand hygiene regulations was not affected by the situation of patients with dystonia in the analyzed group, as well as wearing masks, and in terms of difficulties in performing their usual sensory tricks it was 34%.

13. During the restrictive pandemic period, the majority of participants (80%) did not have access to a different clinic or could not afford the injection. Some (19%) opted for alternative treatments, such as acupuncture.

14. Although access was limited in terms of injectable treatment, only 61% felt their right was violated.

15. The vast majority (51%) of patients had either had COVID-19 vaccination or were due to receive the vaccine (22%). More than half of the patients (58%) were not concerned about the potential pharmacological interactions between the injectable botulinum toxin treatment and the anti-SARS-CoV-2 vaccine.

16. As regards the analysis of quality of life using the EQ-5D scale, in the vast majority for the mobility and self-care subdomains, the patients in the lot did not show any impairment, the activity subdomain being moderately affected for 22% of patients, respectively 30% mild impairment, the subdomain of pain showing moderate impairment in 35% of patients and mild impairment in only 23%. Most patients 35% had no problems with anxiety, but 29% described mild problems and 24% described moderate problems.

17. the analysis of the quality of life by the EQ-5D scale, regardless of age group, subdomains of mobility, self-care and activity showed that there was no impairment, the pain predominantly reported as moderate pain for the age group 50-59 years and very mild for the age group 60-69 years. In terms of gender, women generally did not report problems for mobility and self-care, for activity there were almost equal proportions lack of problems and mild problems, pain being reported as moderate, and the field of anxiety was reported predominantly as problem-free, but also as a result of the lack of problems. let it be moderate anxiety. In men, the results were similar except for the pain subdomain as it predominantly reported severe pain

and the anxiety subdomain that was reported in most cases either as trouble-free or as mild anxiety.

18. As for the analysis of quality of life by the EQ-5D scale for the top 5 most common forms of dystonia, it showed that among women the areas of mobility and self-care in general did not report problems, but the sub-field of activity showed in high percentages slightly affected (33.33%), respectively, moderate impairment (28.89%), and the subdomain of pain and anxiety being mainly reported as moderate impairment. In the case of men, the mobility subdomain had mainly reports of severe impairment (25%).

18. Analysis of the EQ-5D subdomains for the first 5 most common forms of dystonia showed severe impairment of mobility for blepharospasm and torticollis in similar percentages, with complex cervical dystonia having predominantly reported moderate problems. In general, the self-care sub-field was not affected, the activity having relatively homogeneous distributions, and in the case of the pain sub-domain, patients with torticollis having predominantly reported moderate pain.

### **Original contributions of the thesis**

Dystonia is a neurological disease with a strong impact on the quality of life, especially by its invalidating nature with major consequences on the social and professional lives of patients with this suffering. The clinical impact of dystonia is major and extensive because in addition to the purely motor component involved in the disease there are other non-motor aspects that affect the daily life of these patients.

There are multiple studies in the international literature that focus on motor phenomena and neuro-anatomical changes that outline the picture of dystonia, but there are no extensive studies on non-motor manifestations (depression, anxiety, cognitive disorders) that occur in this condition. This doctoral thesis evaluates, using internationally validated and translated questionnaires in Romanian, depression and neurocognitive disorder that may be present in patients with this suffering. The evaluation of non-motor manifestations, in addition to motor manifestations, contributes to a correct definition of the clinical profile of the patient for appropriate treatment.

The personal contribution of the doctoral thesis entitled *Clinical Profile, Evolution and impact on quality of life in idiopathic focal dystonia* is based on 2 clinical studies that analyze various aspects of quality of life in the Romanian patient with dystonia, providing useful and reliable information for both researchers in the field and clinical practice. The development of these two studies was based on the analysis of a large group of patients (n=221) diagnosed by the neurologist with a focus on the study of the quality of life of patients with dystonia and the impact of the COVID-19 pandemic on them. It is worth mentioning that the most recent bibliographic data from the literature (case-control studies, observational studies, controlled studies) were used in the elaboration of these two clinical studies, the results obtained being comparable to those in the medical literature.

The integrative analysis of non-motor manifestations, in the context of which the quality of life assessment of patients with dystonia is the most important, is particularly useful for a coherent therapeutic approach especially in the current conditions in which the cause of these sufferings is not known, despite the accumulated pathogenic progress.

The first study, non-motor manifestations and quality of life in patients with idiopathic dystonia with focal onset, was conducted on a number of 131 patients with a certain diagnosis of dystonia where the evaluation of non-motor elements was performed by internationally validated questionnaires to establish the presence of neurocognitive disorder (MoCA), Depression (PHQ-9) and quality of life (SF-36). The presence of neurocognitive disorder was present in women with progressive dystonia, while depression was present regardless of gender for progressive dystonia. Scores of SF-36 subdomains showed overall much lower values for progressive dystonia compared to stationary dystonia, which is common in clinical practice. The data set out in the doctoral thesis on neurocognitive disorders and comparative depression between the two stationary and progressive forms of disease constitute a major individual contribution of the thesis, in the current situation in which no data on this problem have been published.

Rezultatele obținute în acest prim studiu au fost publicate în articolul *manifestări non-motorii în distonie idiopatică cu debut focal – un studiu pilot din revista Journal of Medicine and Life Vol. 13, numărul 2, aprilie-iunie 2020, pp. 170–174*. de asemenea data premerii au fost prezentate sub forma de poster în 2019 cu titlul *Depresiune și insuficiență cognitivă în distonia focală izolată: Prevalență și factori de risc la un grup de pacienți români*, În cadrul

Congresului Internațional al bolilor Parkinson și tulburărilor de mișcare și tot în 2019 sub forma de poster adult debut distonie focală izolată un studiu descriptiv într-un grup românesc de pacienți la Congresul 5th al Academiei Europene de Neurologie - Oslo 2019.

The second study quality of life and the impact of the COVID-19 pandemic on patients with dystonia was conducted on a batch of 90 patients with dystonia diagnosis, being evaluated for the quality of life during the COVID-19 pandemic, Using as elements of quantification of quality of life on the one hand an internationally validated questionnaire EQ-5D, but also a questionnaire made by the research team in order to understand the quality of life and aimed at the patient with dystonia in treatment with botulinum toxin injection. Thus, 74% of patients did not have access to the attending physician for the regular injection of botulinum toxin treatment, and 80% of patients did not reach another clinic during the pandemic period, highlighting the negative impact on accessibility and addressability to the medical act during the pandemic period. This represents another major personal contribution to the doctoral thesis, as few studies have focused on the difficulty encountered by patients in carrying out the medical act during the pandemic period.

Related to the analysis of quality of life through the EQ-5D scale, overall the areas of mobility and self-care showed no problems, but the subdomains of activity, pain and anxiety showed various changes.

The COVID-19 Pandemic: A study on its impact on patients with dystonia and related conditions treated with botulinum toxin in a tertiary Centre in Romania, modern Medicine, No. 2, Vol. 29 of 2022.

In conclusion, the doctoral paper Clinical profile, evolution and impact on quality of life in idiopathic focal dystonia makes important personal contributions through an extensive analysis on a large group of patients with dystonia, focusing on the clinical profile of the patient, the evolution and evaluation of the quality of life of the patient, along with other non-motor manifestations, for the proper management of patients with this disease.

## 6. Selective bibliography

1. Grütz K, Klein C. Dystonia updates: definition, nomenclature, clinical classification, and etiology. *J Neural Transm.* 2021 Apr 1;128(4):395–404.
2. Di Biase L, Santo A Di, Caminiti ML, Pecoraro PM, Lazzaro V Di. Classification of Dystonia. 2022;
3. Samushiya MA, Ragimova AA, Ivolgin AF, Avseitseva TY, Smolentseva IG, Ivannikova EI. [Sleep disorders in patients with cervical dystonia]. *Zhurnal Nevrol i Psikiatrii Im SS Korsakova.* 2020 Jan 1;120(12):25–9.
4. Monaghan R, Cogley C, Burke T, McCormack D, O’Riordan S, Ndukwe I, et al. Non-motor features of cervical dystonia: Cognition, social cognition, psychological distress and quality of life. *Clin Park Relat Disord.* 2020 Jan 1;4.
5. Tolmacheva VA, Yuzbashyan PG, Petelin DS, Volel BA, Salouhina NI, Nodel MR, et al. Anxiety-depressive spectrum disorders in cervical dystonia. *Neurol Neuropsychiatry, Psychosom.* 2022;14(4):38–43.
6. Moriarty A, Rafee S, Ndukwe I, O’Riordan S, Hutchinson M. Longitudinal Follow-Up of Mood in Cervical Dystonia and Influence on Age at Onset. *Mov Disord Clin Pract.* 2022 Jul 1;9(5):614–8.
7. Junker J, Berman BD, Hall J, Wahba DW, Brandt V, Perlmutter JS, et al. Quality of life in isolated dystonia: non-motor manifestations matter. *J Neurol Neurosurg Psychiatry.* 2021 Jun 1;92(6):622–8.
8. Anandan C, Jankovic J. Botulinum Toxin in Movement Disorders: An Update. *Toxins (Basel).* 2021 Jan 1;13(1).
9. Dressler D, Adib Saberi F, Rosales RL. Botulinum toxin therapy of dystonia. *J Neural Transm.* 2021 Apr 1;128(4):531–7.
10. Ortiz RM, Scheperjans F, Mertsalmi T, Pekkonen E. Comorbidity and retirement in cervical dystonia. *J Neurol.* 2019 Sep 1;266(9):2216–23.
11. Beiu C, Mihai M, Popa L, Cima L, Popescu MN. Frequent Hand Washing for COVID-19 Prevention Can Cause Hand Dermatitis: Management Tips. *Cureus.* 2020 Apr 2;12(4).

12. Erbguth F, Lange R. Sensory trick effect in craniofacial dystonia as one of the possible impacts of wearing face masks during the COVID-19 pandemic. *Neurol Res Pract.* 2021 Dec 1;3(1).
13. Erro R, Scannapieco S, Russo M, Picillo M, Barone P. Impact of COVID-19 on neurological patients attending a botulinum toxin service. *Neurol Sci.* 2021 Feb 1;42(2):433–5.
14. Dressler D, Adib Saberi F. Botulinum toxin therapy in the SARS-CoV-2 pandemic: patient perceptions from a German cohort. *J Neural Transm.* 2020 Sep 1;127(9):1271–4.
15. Neeraja K, Suriseti B, Mol N, Prasad S, Holla V, Kamble N, et al. Impact of Disrupted Botulinum Toxin Therapy in Movement Disorders Due to COVID-19 Pandemic. *Ann Indian Acad Neurol.* 2021;24(6):1001.
16. Kim DD, Kung CS, Perez DL. Helping the Public Understand Adverse Events Associated With COVID-19 Vaccinations: Lessons Learned From Functional Neurological Disorder. *JAMA Neurol.* 2021 Jul 1;78(7):789–90.
17. Matar E, Manser D, Spies JM, Worthington JM, Parratt KL. Acute Hemichorea-Hemiballismus Following COVID-19 (AZD1222) Vaccination. *Mov Disord.* 2021 Dec 1;36(12):2714–5.
18. Salinas MR, Dieppa M. Transient akathisia after the SARS-Cov-2 vaccine. *Clin Park Relat Disord.* 2021 Jan 1;4.



## 7. Scientific papers

1. Mioara Avasilichioaiei; **Ovidiu-Lucian Bajenaru**, (autor correspondent); Natalia Blidaru,; Sorina Neculai,; Liviu Cozma,; Iulia Mitrea,; Delia Tulbă,; Bogdan Popescu, 2022. The COVID-19 Pandemic: a Study on Its Impact on Patients with Dystonia and Related Conditions Treated with Botulinum Toxin in a Tertiary Centre in Romania. *Medicina Moderna - Modern Medicine*. 29. 105-114. DOI:10.31689/rmm.2021.29.2.105. CNCSIS Category B+ journal, ISSN-online 2360-2473, ISSN-L 1223-0472, ISSN-print 1223-0472, Indexed by SCOPUS, EBSCO, DOAJ, CiteFactor, Scipio of UEFISCDI, and INDEX COPERNICUS.

<https://medicinamoderna.ro/the-covid-19-pandemic-a-study-on-its-impact-on-patients-with-dystonia-and-related-conditions-treated-with-botulinum-toxin-in-a-tertiary-centre-in-romania/>

2. **Bajenaru OL**, Popescu-Olaru I, Dumitrescu L, Serban E, Cozma L, Raicu F, Cocos R, Popescu OB. 2020. Non-Motor Manifestations in Idiopathic Dystonia with Focal Onset - A Pilot Study. *Journal of Medicine and Life*, 13(2), 170–174., PMID: 32742509 PMCID: PMC7378344 DOI: 10.25122/jml-2020-0094, ISSN:18443117, 1844122X, factor impact (2022-2023):1,474 , ISSN: Online ISSN 1844-3117, Online ISSN 1844-3109, Print ISSN 1844-122x, indexed by SCOPUS, PubMed, ProQuest, EBSCO, CNCSIS, INDEX COPERNICUS, NLM Unique ID101477617, Publisher Carol Davila University Press.

<https://medandlife.org/all-issues/2020/issue-2-2020/original-article-issue-2-2020/non-motor-manifestations-in-idiopathic-dystonia-with-focal-onset-a-pilot-study/>