CLARICE LISTIK

Classificando a dor crônica nas distonias: um estudo multicêntrico

Versão corrigida
(Versão original encontra-se na unidade que aloja o Programa de Pós-graduação)

Tese apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção do título de Doutor em Ciências

Programa de Neurologia
Orientador: Prof. Dr. Daniel Ciampi Araujo de Andrade

Coorientador: Prof. Dr. Rubens Gisbert Cury

São Paulo

2023

Dados Internacionais de Catalogação na Publicação (CIP)

Preparada pela Biblioteca da
Faculdade de Medicina da Universidade de São Paulo

Listik, Clarice
Classificando a dor crônica nas distonias : um estudo multicêntrico / Clarice Listik. -- São Paulo, 2023.
Tese(doutorado)--Faculdade de Medicina da Universidade de São Paulo.
Programa de Neurologia.
Orientador: Daniel Ciampi Araujo de Andrade.
Coorientador: Rubens Gisbert Cury.

Descritores: 1.Distonia 2.Dor 3.Dor crônica 4.Classificação 5.Mensuração de dor 6.Distúrbios do movimento 7.Psicometria

USP/FM/DBD-234/23

Responsável: Erinalva da Conceição Batista, CRB-8 6755

CLARICE LISTIK

Classifying chronic pain in dystonia: A multicenter study

Corrected version

A Thesis presented to the Department of Neurology of *Faculdade de Medicina da Universidade de São Paulo* to obtain the title of Doctor in Sciences.

Department of Neurology
Supervisor: Prof. Daniel Ciampi Araujo de Andrade

Co-Supervisor: Prof. Rubens Gisbert Cury

Sao Paulo

2023

Listik C. Classificando a dor crônica nas distonias: um estudo multicêntrico [doutorado]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2023.

Aprovado em:

Banca Examinadora

Prof. Dr. _____

Instituição: _____

Julgamento: _____

Prof. Dr. _____

Instituição: _____

Julgamento: _____

Prof. Dr. _____

Instituição: _____

Julgamento: _____

DEDICATION

I would like to dedicate this thesis to my brother Eduardo for his help, and scientific encouragement. Also, to my parents, Marcia and Sergio, for the daily example of determination and ethics and for their unparalleled support.

To people with dystonia, for their help and contribution to this project.

ACKNOWLEDGMENTS

This project was done by many hands, and I would like to acknowledge individuals and groups that helped and supported me before or during this project.

To my brother, **Dr. Eduardo Listik**, for all the help and contribution during all the phases of this project. He contributed to scale development, statistical analysis, manuscript revision, and many other aspects of this project. Thank you.

To **Professor Daniel Ciampi de Andrade** for the guidance, patience, academic inspiration, and attention all the way through this project. Professor Ciampi contributed to everything in this project: from the original idea to the scale development and the many drafts revisions. Thank you.

To **Professor Rubens Gisbert Cury** for his scientific enthusiasm and insight. Professor Cury helped in the scale development and revision of the final manuscript.

To **Dr. Denise Maria Meneses Cury Portela** for her remarkable contribution to this project and her friendship. She is a living example of the Brazilian expression "*não há tempo ruim*". To **Natália Rebeca Alves de Araújo** for her contribution to this project and friendship. Both contributed to recruiting patients, gathering data, and revising the final manuscript. Dr. Portela also helped to gather our project approval at her center. To *Instituto de Ensino Superior do Piaui*, one of the centers that made this project possible.

To **Dr. Flávia de Paiva Santos Rolim** for her unparalleled contribution to this Project, her friendship, and her constant encouragement. Also, Dr. Pedro Rubens Araújo Carvalho, Professor Fernanda Martins Maia Carvalho, and Dr. Rolim contributed to recruiting patients, gathering data, and revising the final manuscript. Dr. Rolim also helped to gather approval at her center for this project. To ***Hospital Geral de Fortaleza (HGF)***, another one of the centers that made this project possible.

To **Professor Sarah Teixeira Camargos,** for the honor of working with you on this project and for the academic inspiration. Professor Camargos helped gather center approval for this project, data collection, and revision of the final manuscript. **To Professor Francisco Cardoso** for his support of this project and the honor of working with you. Professor Cardoso helped with many suggestions for the final manuscript of this project, undoubtedly improving its content. To ***Hospital das Clínicas da Universidade Federal de Minas Gerais (UFMG)***, another one of the centers that made this project possible.

To **Dr. Graziele Costa Santos** for her help gathering center approval for this project and data collection. To **Professor Henrique Ballalai Ferraz**. Thank you for the opportunity and honor of working with you on this project. To ***Universidade Federal de Sao Paulo (UNIFESP)***, another one of the centers that made this project possible.

To **Professor Egberto Reis Barbosa**, **Professor João Carlos Papaterra Limongi,** and **Professor Manoel Jacobsen Teixeira** for their continuous support and inspiration, it is always an honor to work with you. Also, to the ***Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP)***, the main center of this Project and my second home since Medical School.

To **Professor Santiago Perez Lloret** for his help in improving this project, including revising the many phases of this project manuscript.

To **Professor Veit Mylius** and **Professor Florian Brugger** for helping revise the manuscript derived from this research.

To all that dedicated their time and contributed to this project in many different ways: To **Professor Rose Mary Paulo do Nascimento**, **Professor Mauro Cunningham**, **Professor Laura Silveira Moriyama**, **Professor Suzana Curcino Nogueira Lino**, **Professor Ana Mercia Fernandes**, **Dr. Fabricio Vale**, **Dr. Jorge Dornellys da Silva Lapa**, **Dr. Luciana Mendonça Barbosa**, for their help in this project.

To **Professor Clécio de Oliveira Godeiro Júnior**, **Professor Vitor Tumas**, **Dr. Manuelina Mariana Capellari Macruz Brito**, and to **Dr. Rafael Tomio Vicentini Otani**, my thanks.

To **Professors Egberto Reis Barbosa**, **João Carlos Papaterra Limongi**, **Mônica Santoro Haddad**, **Márcia Rúbia Rodrigues Gonçalves**, and all the *Hospital das Clínicas'* Movements Disorders' Family for inspiring me to enter this fascinating field and to the knowledge shared in the weekly outpatient clinic since my Neurology residence. To my friends **Dr. Ana Paula Selga Bertholo**, **Dr. Carina Cura França**, **Dr. Isabela Bruzzi Paraguay**, **Dr. Rafael Bernhart Carra**, **Dr. Anderson Pelichek**, **Dr. Janaína Reis Menezes**, and **Dr. Jacy Parmera**.

To the professors, physicians, and employees of the *Hospital das Clínicas*' Neurology Department, especially to **Ms. Sueli Martins**, **Mrs. Reiko Uchizono Simomura**, **Mrs. Valdenira dos Santos Ferreira**, **Mrs. Vanessa Ramos Cardoso**, and **Ms. Thais Fiqueira**. Thank you for the knowledge shared and the inspiration to improve.

To all **people with dystonia**, especially those who could contribute their time to this project. People with dystonia have extraordinary determination and perseverance; you are the definition of inspiration.

To my Family, my parents, **Dr. Marcia Listik** and **Dr. Sergio Listik**. My brother **Dr. Eduardo Listik**. My aunts and uncles, **Dr. Myrian Sapucahy Lins**, **Roberto Listik**, **Eliude José Bianchi** and **Vivian Manso Sousa**. To my grandparents (*in memoriam*), **Ruth Francisconi**, **Anna Listik**, **Luiz Sapucahy Cavalcanti Lins,** and **Ajzik (Arthur) Listik**. To my cousins **Dr. Mirella Sapucahy de Castro** and **Noah Manso de Sousa Listik**.

EPIGRAPH

“Ideas and only ideas can light the darkness.”

Ludwig Heinrich Edler von Mises (1881–1973)

“It takes considerable knowledge just to realize the extent of your own ignorance.”

Thomas Sowell (1930-)

"I was taught that the way of progress was neither swift nor easy.”

Marie Curie (1867-1934)

RESUMO

Listik C. Classificando a dor crônica nas distonias: um estudo multicêntrico [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2023.

Introdução: As distonias são associadas a sintomas não-motores incapacitantes como a dor crônica (DC). A DC é prevalente na distonia e impacta significativamente a qualidade de vida (QV). Não há uma ferramenta validada para avaliar a DC nas distonias, fato que dificulta o tratamento e manejo da dor. **Objetivo:** Desenvolver uma classificação de DC e sistema de pontuação para as distonias. **Método:** Um grupo multidisciplinar foi estabelecido para desenvolver a *Dystonia-Pain Classification System* (*Dystonia-PCS*) para classificar DC como relacionada ou não à distonia e fornecer um escore de gravidade de dor englobando intensidade de dor, frequência, e impacto na vida diária. Após, pacientes avaliados consecutivamente com distonias hereditárias/idiopáticas de qualquer distribuição, com ou sem DC foram recrutados num estudo de validação multicêntrico transversal. A *Dystonia-PCS* foi comparada com escalas clássicas de dor, humor, QV e distonia (*Brief Pain Inventory-BPI*, *Douleur Neuropathique-4 questionnaire* (DN4), *Hospital Anxiety and Depression Scale*, EuroQol-5D-3L e *Burke–Fahn–Marsden Dystonia Rating Scale*). **Resultados:** A DC esteve presente em 81 dos 123 pacientes recrutados. A DC principal foi diretamente relacionada à distonia em 82,7% dos pacientes, agravada pela distonia em 8,64%, e não-relacionada à distonia em 7,41%. A *Dystonia-PCS* teve excelente escore intra-avaliadores (ICC 0,941) e inter-avaliadores (ICC 0,867). Além disso, ela foi significativamente correlacionada ao subescore de dor da EuroQol-5D-3L ($\rho = 0,635$; $p < 0,001$), aos subescores de gravidade e interferência do BPI ($\rho = 0,553$; $p < 0,001$ e $\rho = 0,609$; $p < 0,001$, respectivamente), e ao escore DN4 ($\rho = 0,397$; $p < 0,001$). **Conclusão:** A *Dystonia-PCS* é uma ferramenta confiável para categorizar e quantificar o impacto da DC nas distonias e pode melhorar o desenho de estudos clínicos e o manejo da DC na distonia.

Palavras-chave: Distonia. Dor. Dor crônica. Classificação. Mensuração de dor. Distúrbios do movimento. Psicometria.

ABSTRACT

Listik C. Classifying chronic pain in dystonia: a multicenter study [thesis]. Sao Paulo: “Faculdade de Medicina, Universidade de São Paulo”; 2023.

I**ntroduction:** Dystonia is associated with disabling non-motor symptoms like chronic pain (CP). CP is prevalent in dystonia and significantly impacts the quality of life (QoL). There is no validated tool for assessing CP in dystonia, which substantially hampers pain treatment and management. **Objective:** To develop a CP classification and scoring system for dystonia. **Methods:** A multidisciplinary group was established to develop the Dystonia-Pain Classification System (Dystonia-PCS) to classify CP as related or unrelated to dystonia and to provide a pain severity score encompassing pain intensity, frequency, and impact on daily living. Then, consecutive patients with inherited/idiopathic dystonia of any distribution, with or without CP, were recruited in a cross-sectional multicenter validation study. Dystonia-PCS was compared to classic pain, mood, Qol, and dystonia scales (Brief Pain Inventory-BPI, Douleur *Neuropathique-4 questionnaire*-DN4, Hospital Anxiety, and Depression Scale, EuroQol-5D-3L and Burke–Fahn–Marsden Dystonia Rating Scale). **Results:** CP was present in 81 of 123 recruited patients with dystonia. The main chronic pain was directly related to dystonia in 82.7% of patients, aggravated by dystonia in 8.8%, and non-related to dystonia (7.5%). Dystonia-PCS had excellent intra-rater (ICC 0.941) and inter-rater (ICC 0.867) reliability. In addition, it correlated significantly with EuroQol-5D-3L’s pain subscore ($\rho = 0.635$, $p < 0.001$), BPI severity and interference subscores ($\rho = 0.553$, $p < 0.001$ and $\rho = 0.609$, $p < 0.001$, respectively), and DN4 score ($\rho = 0.397$, $p < 0.001$). **Conclusion:** Dystonia-PCS is a reliable tool to categorize and quantify CP impact in dystonia and will help to improve clinical trial design and management of CP in dystonia.

Keywords: Dystonia. Pain. Chronic pain. Classification. Pain measurement. Movement disorders. Psychometrics.

LIST OF FIGURES

LIST OF TABLES

LIST OF INITIALISMS

Initial	Definition
BFMDRS	Burke-Fahn-Marsden Dystonia Rating Scale
BPI	Brief Pain Inventory
BPIi	BPI interference subscore
BPIs	BPI severity subscore;
CAPPesq	*Comissão de Ética para Análise de Projetos de Pesquisa*
CD	Cervical dystonia
CDT	Cold detection threshold
CONEP	*Conselho Nacional de Ética em Pesquisa*
CP	Chronic pain
CPT	Cold pain threshold
DBS	Deep brain stimulation
DC	Dor crônica
DN4	*Douleur Neuropathique-4*
DNMSQuest	The Dystonia Non-Motor Symptoms Questionnaire
Dystonia-PCS	Dystonia-Pain Classification System
EQ	EuroQoL-5D-3L
EQ-VAS	EuroQol's Visual Analogue Scale
EuroQoL-5D-3L	European Quality of Life 5 Dimensions 3 Level Version
GABA	Gamma-aminobutyric acid

GPi	*Globus pallidus internus*
HADS	Hospital Anxiety and Depression Scale
HC-FMUSP	*Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo*
HGF	*Hospital Geral de Fortaleza*
HV,	Healthy volunteers
ICC	Intraclass Correlation Coefficient
ICD-11	International Classification of Diseases-11
MDT	Mechanical detection thresholds
MPT	Mechanical pain thresholds
MRgFUS	Magnetic resonance-guided focused ultrasound
MRI	Magnetic resonance imaging
NMS	Non-motor symptoms
NPSI	Neuropathic Pain Symptom Inventory
OCD	Obsessive-compulsive disorder
OR	Odds Ratio
PD	Parkinson’s disease
PD-PCS	Parkinson’s Disease Pain Classification System
PwD	People with dystonia
QoL	Quality of life
QST	Quantitative sensory testing
QV	*Qualidade de vida*
REDCap	Research Electronic Data Capture
REM	Rapid Eye Movements

S.D.	Standard deviation
SPSS	Statistical Package for the Social Sciences software
STN	Subthalamic nucleus
SuC	Pain rating to experimental pain cold stimulus
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
TWSTRS	Toronto Western Spasmodic Torticollis Rating Scale
UFMG	*Universidade Federal de Minas Gerais*
UNIFESP	*Universidade Federal de Sao Paulo*
VAS	Visual analogue scale
VIM	*Ventralis intermedius nucleus*
WDT	Warm detection threshold

SUMMARY

1 INTRODUCTION

Dystonia is a movement disorder of inherited, acquired, or idiopathic etiology.[1] Treating dystonia is part of the everyday life of neurologists since inherited/idiopathic dystonia has a prevalence of 30.85 per 100,000 people.[2] It also represents roughly 20% of cases seen by movement disorders specialists.[3] The disorder is challenging because it presents both motor and non-motor symptoms.

Non-motor symptoms (NMS) are frequent in dystonia and impact patients' quality of life (QoL).[4, 5] Chronic pain (CP) is pain that lasts or recurs for longer than three months. [6, 7] It is present in up to 30% of the general population. [6, 7] It is prevalent in people with dystonia (PwD) and is not necessarily related to dystonia's severity.[8-10] CP frequently occurs even after deep brain stimulation (DBS) for dystonia,[11] a traditional treatment for refractory dystonia. In cervical dystonia (CD), emotional well-being and pain significantly impact QoL more than dystonia's severity.[12] Pain significantly contributes to disability, which affects daily life and work.[13]

PwD have both peripheral and central sensory abnormalities, with abnormal processing of the nociceptive stimuli.[10, 14-19] Also, the pain's modulatory system is abnormal in dystonia.[14] Therefore, pain in dystonia does not have only a muscle-based (i.e., muscologenic) mechanism,[13] and it is likely multifactorial. As seen in both botulinum toxin and DBS studies, dystonia's motor treatment improves pain,[5, 20] but pain still remains a problem for many PwD even after the established motor treatment.

CP has been less evaluated in dystonia than in other movement disorders like Parkinson's Disease (PD).[21] PD has many studies focusing on CP classification and on understanding how treatment impacts pain.[22-28]

At the same time, there is no specific way to measure CP in dystonia and no validated tool for PwD.[21] Through a literature review, we found no specific

classification system for CP in dystonia,[21] nor a way to quantify CP's impact. This lack of assessment tools leads to few investigations and trial-based data on managing pain in dystonia, creating a vicious cycle that may perpetuate patients' suffering and risk of iatrogenic outcomes.[21] Also, being able to classify if CP is directly related or unrelated to dystonia is the base to help understand the mechanism of pain and its treatment.

Considering this, we established a multidisciplinary group that aimed to develop a pain classification system for dystonia that also shows the pain's impact.

1.1 Justification

NMS are crucial in dystonia and greatly impact QoL.[4, 9, 29, 30] Pain is one of the most prevalent and relevant NMS.[4] There is no validated tool for CP evaluation in dystonia, which hampers the development of new strategies for treatment and management.

2 OBJECTIVES

2.1 Main Objective

- To develop a multidisciplinary CP classification system for dystonia.

2.2 Specific Objectives

- To examine the scale's psychometric properties and validity.
- To develop a score that can evaluate CP's impact in PwD.

3 REVIEW OF THE LITERATURE

3.1 Definition and clinical classification

Dystonia means “altered muscle tone”[31] and originates from the modern Latin *dys*- and the Greek *tonos*.[32] Hermann Oppenheim first described it as “*dystonia musculorum deformans.*”[33]

Since its first description, dystonia’s explanations have frequently varied between functional and organic sources.[3, 34] Many eminent neurologists highlighted a “psychogenic” origin for the disease, partially because of stress-related deterioration of symptoms, the presence of sensory tricks, and psychopathology influence.[3] Charcot reported a patient with CD that began after economic problems.[33] Edouard Brissaud coined the term “*torticollis mental”* reasoning as evidence of his patient’s sensory trick, also known as *geste antagoniste*.[35]

The *Réunion Neurologique Internationale Annuale* (1929) took place with a major agreement that dystonia was not “organic”. Nevertheless, Meige tried to showcase his belief that focal cranial dystonias were a basal ganglia disorder.[33]

After the discovery of a hereditary pattern of some dystonias[36] along with the finding of isolated dystonia’s first *locus* (9q32-34)[37] and later gene[38] *DYT1* (DYT-*TOR1A*[39] in current terminology), the organic cause gained force. There was also evidence given by procedures like thalamotomy and pallidotomy, which improved dystonia’s motor symptoms.[40]

David Marsden described types of focal dystonias initiated in adult life, like blepharospasm. [31] He discovered abnormal activation of agonists and antagonists muscles, typical of dystonias, by means of neurophysiological methods.[41] Interestingly, though most dystonias are organic, it is also the second most frequent type of functional movement disorder.[42]

Most recently, Albanese et al. (2013) defined dystonia as:[43]

> "(…) a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation". (Albanese et al, 2013, p. 866)

It is essential to highlight that dystonia's diagnosis is clinical and based primarily on phenomenology. The current classification (Table 1) has clinical characteristics and etiology axes.[43]

Table 1 — Dystonia's Classification. The current dystonia classification by Albanese et al.[43, 44]

Axis I. Clinical characteristics		
Clinical characteristics of dystonia	Age at onset	1. Infancy (birth to 2 years) 2. Childhood (3 to 12 years) 3. Adolescence (13 to 20 years) 4. Early adulthood (21 to 40 years) 5. Late adulthood (> 40 years)
	Body distribution	1. Focal 2. Segmental 3. Multifocal 4. Generalized (with or without leg involvement) 5. Hemidystonia
Clinical characteristics of dystonia	Temporal pattern	Disease course 1. Static 2. Progressive Variability 1. Persistent 2. Action-specific 3. Diurnal 4. Paroxysmal
	Associated features	Isolated dystonia or combined with another movement disorder 1. Isolated dystonia 2. Combined dystonia The occurrence of other neurological or systemic manifestations

Table 1 — Dystonia's Classification (continuation).

Axis II. Etiology		
Etiology	Nervous system pathology	Evidence of degeneration
		Evidence of structural (often static) lesions
		No evidence of degeneration or structural lesion
	Inherited or acquired	**Inherited**
		Autosomal dominant
		Autosomal recessive
		X-linked recessive
		Mitochondrial
		Acquired
		Perinatal brain injury
		Infection
		Toxic
		Drug
		Vascular
		Neoplastic
		Brain injury
		Psychogenic
		Idiopathic
		Sporadic
		Familial

According to their distribution, dystonias can be classified as focal, segmental, multifocal, generalized, or hemidystonia.[1] They are also classified as isolated (i.e., forms that have only dystonia and/or dystonic tremor) or combined (formerly known as dystonia-plus) that have other movement disorders associated (e.g., myoclonus or parkinsonism).[1]

Regarding etiology, the dystonias may be inherited (e.g., autosomal dominant, autosomal recessive, X-linked, or mitochondrial); acquired (e.g., infections, perinatal brain injury, neoplastic, and others); or idiopathic. The most recent classification system of the monogenic forms of dystonias uses the gene

associated with dystonia (e.g., DYT-*TOR1A*, DYT-*THAP1*, and DYT-*PRKRA*),[39] as opposed to the formerly used DYT plus a sequential number (e.g., *DYT1*, *DYT6*, and *DYT16*, respectively).[45]

It is essential to know this classification system because the motor treatment rationale, as well as the treatment outcome, is very different depending on the distribution of the dystonia (generalized *versus* focal/segmental dystonias), as well as depending on the etiology (inherited/idiopathic *versus* most of the acquired dystonias).

3.2 Epidemiology

Dystonias are the third most frequent movement disorder.[46] They are a heterogeneous group of disorders[47] but are more prevalent than other well-known neurological disorders, such as motor neuron disease.[48]

A recent systematic review analyzed studies published between 2010 and 2022 and found an estimated prevalence for idiopathic or inherited isolated dystonia of 30.85 per 100,000 people.[2] A previous systematic review of “primary dystonia” (using the former classification)[49, 50] reviewed studies published between 1985 and 2010 that found an overall prevalence of 16.43 per 100,000 people.[47] The most recent review found no difference in prevalence regarding when the study was published.[2]

Cervical and hand idiopathic dystonias usually have an onset between 30-50 years, while cranial dystonias (e.g., blepharospasm or oromandibular dystonia) and laryngeal dystonias (also known as spasmodic dysphonia/dystonia) begin in the fifth or sixth decade.[51] The prevalence of CD is estimated to be 9.95 per 100,000 people; of blepharospasm 2.82 per 100,000 people; of laryngeal dystonia 0.40 per 100,000 people; of upper limb dystonia 1.27 per 100,000 people; and of oromandibular dystonia 0.57 per 100,000 people.[2]

For acquired dystonias, epidemiological studies are scarce. Tardive dyskinesia has a prevalence of 25.3%.[52] In a cross-sectional study with children diagnosed with cerebral palsy, dystonia was prevalent in both spastic and dyskinetic subtypes of cerebral palsy.[53]

An epidemiology study in the city of Hannover revealed that most of the PwD had CD (42%). In comparison, 15% had blepharospasm, 9% writer's cramp, 6% tardive dystonia, 5% musician's dystonia, 5% psychogenic dystonia, 4% generalized dystonia, 4% spasmodic dysphonia, 3% segmental dystonia, 3% arm dystonia and 2% oromandibular dystonia. Leg dystonia and hemidystonia were rare.[54]

Interestingly, dystonias are more prevalent in women.[2, 51] Craniocervical dystonia (CD, spasmodic dysphonia, blepharospasm, oromandibular dystonia, and Meige syndrome) is more common in women, with a male-to-female range of 1:1.6 to 1:3.8.[55] Nevertheless, most focal task-specific dystonias (musician's, writer's, and golfer's cramps) are more typical in men.[55] In generalized dystonia, no sex predominance has been reported, except for DYT-*GCH1*, which is more frequent in females.[55]

3.3 Pathophysiology

The pathophysiology of dystonia is complex and not fully elucidated. The identified core neurophysiological alterations are:[56, 57]

i. A reduction of inhibition: Inhibition abnormalities exist at many levels of the central nervous system[58, 59] with documentation of a loss of surround inhibition[56, 60, 61], loss in short and long intracortical inhibition, and shortening of the silent period.[56] Loss of inhibition may justify the co-contraction of antagonists, the dysfunction of the cortico-striatum-thalamo-cortical circuitry, and the hardship in selecting the right movement and inhibiting the inappropriate one.[56]

ii. Abnormal neuroplasticity: it leads to dysfunctional connections. In CD, if neuroplasticity is more intense, there is worse impairment and a better DBS outcome.[62]

iii. Abnormalities in the sensory system: abnormalities in the organization of the somatosensory cortical maps may lead to alteration in the body parts' cortical representation.[10] Motor-sensory integration and sensory processing alterations may also play a role.[19] Also, sensory tricks are able to alter dystonic movements.[18] They, otherwise known as "*geste antagoniste*", induce partial or total improvement of the dystonia. Physiology studies show that these tricks minimize the unbalance of cortical facilitation/inhibition.[63]

There are also structural abnormalities, such as an increment in the density of grey matter in the primary sensory cortex and an enlargement of the basal ganglia.[64] Functional alterations, such as anomalous activity in the sensorimotor cortex, supplementary motor area, and premotor cortex during motor tasks, and intensification in the rest glucose metabolism in the lentiform nucleus and the premotor cortex, have also been observed.[64]

3.3.1 Dystonia *as a circuit disorder*

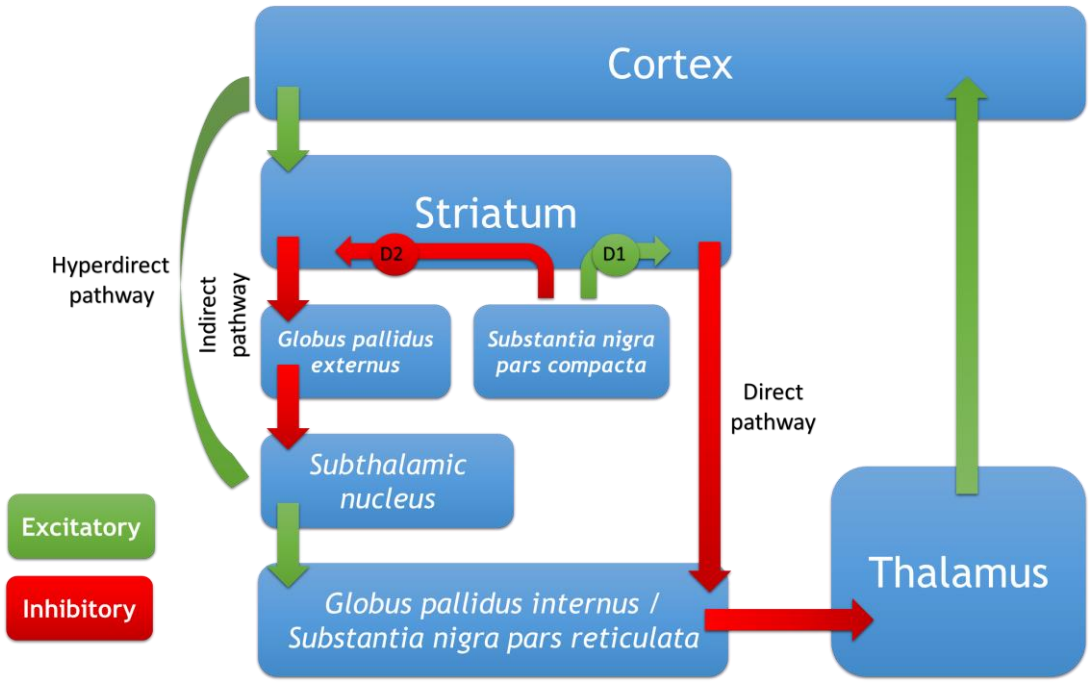
Dystonia is a network disorder involving the basal ganglia-thalamo-cortical and cerebellum-thalamo-cortical circuits.[3, 65, 66]

The classic basal ganglia model (Figure 1) describes that the direct pathway facilitated movement by minimizing the inhibitory output from the *globus pallidus internus* (GPi). The indirect pathway's activation would increase inhibitory outputs and reduce movement.[3] In this model, dystonia results from a disproportion of the direct and indirect pathways reducing the inhibition of the thalamus and, therefore, leading to motor cortex excitability.[67, 68]

Nevertheless, DBS's recording of local field potentials shows abnormal spatial and temporal firing patterns of activity within the GPi and other nuclei.[3]

Modern theories suggest that these abnormal patterns are responsible for involuntary movements in dystonia.

Figure 1 — The classical model for the basal ganglia connections. The cortical input to the basal ganglia occurs through cortico-striatum and cortico-subthalamic projections. The projections from the basal ganglia to the cortex (output) originate from the *globus pallidus internus* and the *substantia nigra pars reticulata*, passing through the ventral thalamic nuclei. The direct pathway is monosynaptic and inhibitory, while the indirect excitatory pathway is polysynaptic. The hyperdirect pathway is also illustrated. D1 and D2 are dopaminergic receptors.[44]



DBS of both GPi[69-73] and the subthalamic nucleus (STN)[74-77] are already a traditional motor treatment option with good motor improvement in many forms of dystonia, especially inherited/idiopathic isolated generalized dystonia,[72, 73, 78] myoclonus-dystonia,[78] CD [72, 73, 78] and tardive dystonia[74, 78].

The cerebellum-thalamo-cortical circuit plays a role in dystonia, with neuroimaging and animal studies indicating abnormalities in this circuit.[79, 80] Rodent models have shown that neuronal dysfunction originating in the cerebellum can drive dystonic movements.[81] A recent review on the effect of cerebellar neuromodulation found nine studies totaling 112 patients with CD or focal hand dystonia.[82] Only patients with focal dystonia have participated in

studies that used Transcranial Magnetic Stimulation (TMS) or transcranial direct current stimulation (tDCS).[82] Patients with CD showed an improvement of up to 39%, while patients with focal hand dystonia had no improvement.[82] The cerebellum is a promising new target for DBS,[83] as there are case reports[84, 85] and series[86] that reveal an improvement of dystonia on both idiopathic[84] and acquired dystonias.[85, 86]

3.4 Dystonia's motor symptoms

Dystonia's main motor symptoms are the movements and/or postures typical of the disease.[3] They can be (i) focal like blepharospasm, in which there is involuntary blinking and eyelid closure, (ii) segmental like CD, in which there is abnormal muscle contraction of specific head and neck muscles (e.g., laterocollis, torticollis, anterocollis, etc.), (iii) multifocal in which two non-contiguous or more (contiguous or not) body regions are involved in the movements and/or postures, (iv) generalized in which the trunk and at least two other sites are involved, and (v) hemidystonia in which more body regions restricted to one body side are involved (usually occurs in acquired forms of dystonias due to contralateral brain lesions).[1] Dystonic tremor can also be a motor feature in dystonia. It is rhythmical but inconstant and can precede the dystonic posture.[3]

Another common feature is the overflow, where the dystonic movement spreads to adjacent or other body areas during the movement of the primarily affected body part.[3] One interesting overflow phenomenon is mirror dystonia, in which there is unplanned dystonic movement in the contralateral limb when a voluntary movement is performed on the other side.[3]

The sensory trick, also known as *geste antagoniste,* is typical of dystonia and is defined as a voluntary movement that mitigates the dystonic posture (e.g., a light touch to the chin can temporally correct the patient's torticollis).[3, 35]

Adult-onset idiopathic dystonias may affect different body areas, and the most common ones are the cervical and cranial regions and the upper limb.[87] Dystonia may remain restricted to a particular body region or spread to different body areas.[88] A recent international cohort has evaluated the risk of dystonia's advancement in adult-onset isolated focal dystonias.[88] Only patients with dystonia onset in the neck, upper face, hand, or larynx at the beginning of the symptoms were evaluated. The motor spread was seen in 50% of blepharospasm, 8% of CD, 17% of hand dystonia, and 16% of laryngeal dystonia patients. Patients with blepharospasm usually spread to the oromandibular region and the neck. In contrast, CD patients typically have a spread to the upper limb area, and patients with upper limb dystonia or laryngeal dystonia show an advancement to the neck.[88] Family history of dystonia was a risk factor for the spread of dystonia and alcohol responsiveness.

3.5 Non-motor symptoms in dystonia

Despite being less apparent than the motor symptoms in PwD, NMS are increasingly identified/perceived to contribute to the disorder, impacting patients' QoL, education, and work life.[89] Thus, NMS are now progressively the aim of many studies in dystonia.[8, 21, 29, 90-98]

NMS spectrum is vast, comprising: pain, psychiatric symptoms, cognitive issues, and sleep disorders, among others.[4] Most of NMS's studies/cohorts are done in PwD already in established motor treatments.[99] Nonetheless, the NMS are still prevalent despite them.[89, 99]

Most PwD have at least one NMS[67, 99], with one study reporting that more than half of its sample has more than 5 NMS (moderate and severe burden levels of NMS).[99] NMS differ depending on the type of dystonia and even in the different genetic dystonias.[92]

PwD may have worse QoL than other people. Still, pain and psychiatric symptoms like depression and apathy are the main driving force behind poor QoL, while motor symptoms' severity do not appear as such in some studies.[8]

3.5.1 Pain in people with dystonia

CP has many causes and is among the most incapacitating disease in the world.[100] CP affects up to 30% of the general population,[6, 7] and in 2006, it was reported that 19% of adults had a CP condition that would significantly impact their QoL.[101]

The experience of pain includes the quality and intensity of the peripheral stimulus and is influenced by pain's modulatory systems.[102] Pain is variably felt due to diverse psychological and cultural backgrounds. Moreover, there are endogenous pain modulatory systems able to modulate pain through descending modulatory pathways that may both facilitate and inhibit pain. [102]

Pain in PwD is disabling and impacts QoL.[103, 104]. There are no specific criteria or classification tools for pain in dystonia[21, 105], probably due to the scarcity of studies focusing on this topic.[92] Pain is prevalent in dystonia, affecting up to 90% of patients, depending on the type of dystonia.[20, 103]

Compared to other dystonia types, pain is most prevalent in individuals with CD.[106, 107] In these patients, pain is usually located in the neck, head, or in the ipsilateral (i.e., to the side of the head rotation) arm,[9] and almost two-thirds of them need daily analgesia at some point during the disease.[108] In CD, emotional well-being and pain extensively impact QoL, being more significant than motor severity.[12] There is a lack of correlation between pain and motor severity in CD.[8, 12, 109] In patients with CD that underwent botulinum toxin injection for a mean of 9 years, 20.7% referred none/low satisfaction with the therapy. In this subgroup, patients had a higher incidence of CD and higher scores on the Visual Analogue Scale (VAS).[110]

In a study with PwD with idiopathic focal or segmental dystonia, patients were 2.5 more likely to have pain than healthy volunteers.[8] Their pain was also more intense. Lastly, individuals with CD and writer's cramp had pain in the location of their dystonia, while people with blepharospasm described pain in other body areas.

As seen above, most studies on pain evaluate patients exclusively with CD or in a mixed cohort with other types of dystonia.[11, 14] Small studies have evaluated other focal dystonias. A small study with people with spasmodic dysphonia showed a higher burden of throat pain, depression symptoms, and insomnia when compared to healthy subjects.[111] In blepharospasm, more than one-third of patients described eye pain.[112] A cohort of 33 patients with isolated generalized dystonia found that patients did not frequently describe pain when compared to reports from focal dystonias like CD.[113]

Concerning acquired dystonias, pain data is even more deficient. A recent community-driven research agenda study concluded that one of the top 10 research themes for dystonia in cerebral palsy was to improve ways to determine the best treatment for pain in these patients.[114]

3.5.1.1 The possible reasons behind pain in dystonia

It has been long believed that pain in PwD would be due to motor over-recruitment and the subsequent activation of muscle, joint, and *fascia* nociceptors. However, some critical factors suggest that this "musculogenic" hypothesis may not thoroughly explain the higher prevalence of CP in PwD. For example, it has been shown that there is no direct correlation between dystonia's motor severity and pain intensity.[109] Also, some efficacious treatments to control dystonic movements, such as botulinum toxin and DBS, may not completely control pain in PwD, which may persist despite improvement of motor symptoms.[11, 89]

PwD have both peripheral[14-17] and central[10, 18, 19] sensory abnormalities with defective processing of nociceptive stimuli integration.[115]

Also, another component that influences pain in PwD is that the basal ganglia are responsible for the integration of motor, emotional, autonomic, and cognitive processes, probably including mood and pain.[116] The thalamo-cortico-basal ganglia circuits integrate different responses to pain, whether emotional, motor, or cognitive.[5]

Despite many people reporting pain, daily clinical sensory and neurophysiological tests are normal.[18] However, it has been shown that in focal hand dystonia, there might be abnormalities in graphesthesia.[117] Misrepresentation of body parts can play a role in pain mechanisms [118] and there are abnormal processing and altered spatial and temporal discrimination[10] of tactile stimuli.[19, 118] Studies show that usual dystonia treatments, such as botulinum toxin[119] and DBS[120], do not change this abnormal temporal discrimination. It is important to highlight that depression and sleep alterations, common NMS in dystonia may also influence pain.[9, 121]

Quantitative sensory test (QST)[15] evaluates several sensory phenomena such as cold, warm, pain, pressure, and vibration. Studies that evaluated PwD through QST (Table 2), like Paracka et al. (2017), assessed people with focal, segmental, and generalized dystonia.[15] There were subtle sensory abnormalities in dystonia: there was a lower cold detection threshold (CDT) and an increased dynamic mechanical allodynia. Moreover, there was also subtle alterations even in body parts without dystonia. Interestingly, no relation between QST abnormalities and dystonia's severity was found.

In writer's cramp, PwD had increased CDT, warm detection threshold (WDT), and mechanical pain thresholds (MPT). The dystonic limb had higher CDT and WDT than the unaffected one.[16]

The lower pain threshold might help explain pain in dystonia.[9] A twice lower pressure pain threshold was previously described for PwD.[17] This study[17] also identified a lower pain threshold in non-dystonic muscles, supporting the possibility of altered pain processing in PwD.

The abnormal sensory thresholds in PwD were not affected by DBS.[14] Patients had an increased mechanical detection threshold (MDT) and MPT,

regardless of whether DBS was switched on. Nevertheless, pain modulation was remarkably low in dystonia and tended to be aggravated by DBS. These findings might indicate that the analgesic effects after DBS implantation may relate to changes in the central processing of nociceptive inputs and not on short-duration changes in cutaneous sensory thresholds.[14]

Tinazzi et al. (2019) also suggested dysfunction of the descending pain inhibitory pathways in dystonia through another type of conditioned pain modulation protocol in patients with CD.[122] Interestingly, this impairment was seen in patients both with and without pain.

Table 2 — Studies that used QST in dystonia.

Study	Sample	DBS	Main Findings
Paracka et al. (2017)[15]	Twenty patients with inherited or idiopathic dystonia (8 with generalized dystonia, 5 with segmental dystonia with upper limb involvement, and 7 with cervical dystonia, CD).	no	• Decreased CDT and allodynia on both hands (worse in the limb with dystonia); • CD: reduced CDT, WDT, increased allodynia (hand); • Increased CPT and allodynia (shoulder).
Suttrup et al. (2011)[16]	Ten patients with idiopathic hand dystonia.	no	• Increased WDTs, CDTs, and MPT; • Increased WDTs and CDTs in the intraindividual comparison.
Lobbezoo et al. (1996)[17]	Nine patients with CD.	no	• Pain-pressure thresholds two-time lower than HV.
Listik et al. (2021)[14]	Sixteen patients with inherited or idiopathic dystonia (14 with generalized dystonia and 2 with segmental dystonia).	yes	• Increased MDT and MPT were higher in the patients, regardless of the DBS conditions; • Increased CPT and SuC in patients in the on-DBS condition.

Abbreviations: QST: quantitative sensory test; CDT: cold detection threshold; WDT, warm detection threshold; CD: cervical dystonia; CPT, cold pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; HV, healthy volunteers; SuC: pain rating to experimental pain cold stimulus. The table was used with modifications from Listik et al. (2020).[44]

3.5.1.2 How is pain evaluated in studies focusing on PwD?

Pain in dystonia is usually reported in both DBS[5] and botulinum toxin studies[20, 123], generally using the pain subitems of QoL scales[89] or the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)[123] or even unidimensional scales like the VAS.[4, 20]

Another point is that most studies that report pain in dystonia focus only on focal and segmental dystonia, more commonly CD.[5] In this specific type, some studies show that up to 90% of patients have pain.[20] The TWSTRS is a scale specific to CD. It has a pain subitem[124] in which the rater scores the pain's severity (for the worst, best, and usual pain), the duration of pain, and its disability. It does not discriminate whether the pain is chronic or acute since it reports symptoms experienced during the previous week. The Dystonia Non-Motor Symptoms Questionnaire (DNMSQuest)[67] is also validated for CD. One question addresses pain if the patient has an "unpleasant sensation such as numbness, tingling or pins, and needles in the body area or nearby the body area of your dystonia."

Some papers[99] have used the NMS questionnaire for Parkinson's disease,[125] with only one subitem that addresses pain as "unexplained pains (not due to known conditions such as arthritis)."

Though some papers describe PwD's pain, they usually label it solely as "pain" without specifying if the patient has CP, an essential aspect of understanding, studying, and treating pain. Also, patients usually have specific pain syndromes like low back pain,[126] headache,[127, 128] and maybe even neuropathic pain. This is not often specified in most papers focusing on dystonia. This information is vital because the same disease (PD,[129] stroke,[130] and other conditions[131]) may cause different pain syndromes; dystonia fits this rule and is no exception. Pain treatment is guided by the type of pain syndrome the patient has, not the primary disease diagnosis.

Some patients maintain pain even after their motor treatment.[11] These patients must be treated according to their specific pain syndrome, which is impossible without a more in-depth view of the experienced pain.

3.5.2 Psychiatric impairment in dystonia

Different studies have shown the increased presence of depression, anxiety, obsessive-compulsive disorder (OCD), phobias, eating disorders, self-harm/suicidal ideation, and substance abuse across different dystonia types, with depression and anxiety being the most common.[29, 90-92, 95, 96] Both depression and anxiety have been associated with the burden of the disease and reduced QoL, self-esteem, and increased disability.[98, 132]

They have been shown to affect patients with focal (including blepharospasm, writer's cramp, laryngeal dystonia, and other limb dystonias),[8, 111, 133] segmental (CD)[8] and generalized dystonias.[113] Interestingly, psychiatric diagnoses antedated dystonia's motor symptoms.[94, 134, 135]

As in most areas of dystonia research, most studies focus on focal and segmental dystonia, more commonly CD.[8, 98, 113, 132, 133]

Depression is twice more likely (OR: 1.77; 95% CI:1.44–2.19) to be diagnosed in idiopathic dystonia patients than in the general population.[136] This subset of patients also has an elevated risk of suicidal attempts (80%) or deaths.[136] A 2021 meta-analysis found that depressive disorders had a prevalence of 35.8% in CD, 28.4% in cranial dystonia (like blepharospasm or oromandibular dystonia), and 35.1% for mixed forms of adult-onset idiopathic dystonias.[137] These findings reveal higher rates of depression in these patients compared to the general age-matched population (3-15%).[137] Other more prevalent neurological diseases have similar statistics[137]: PD, 18–27%;[138] multiple sclerosis, 26–35%;[139] epilepsy, 20–28%,[140] and dementia, 20–37%.[141]

In generalized dystonia, patients showed significantly higher scores on depression and anxiety scales. The psychiatric scales did not correlate to motor severity or the dystonia's duration.[113]

Anxiety was also recently systematically reviewed.[142] The overall prevalence of anxiety was 40% in CD, 25% for cranial dystonias, 33.3% for mixed adult-onset isolated dystonias, 26% for laryngeal dystonias, and 32% for upper limb dystonias.[142] Social phobia was the most prevalent anxiety disorder.[142]

Regarding patients with genetic dystonias, most studies focus on DYT-*SGCE* and DYT-*GCH1*.[91] The myoclonus-dystonia has higher OCD and psychosis than the other dystonia forms.

3.5.3 Cognitive, sleep, and other issues

Several studies have evaluated cognition through detailed neuropsychological tests and found mildly significant deficits in executive, attentional and visuospatial function.[9] It is hard to establish if those alterations impact daily life from the current evidence because it is not consistently replicated. A recent meta-analysis evaluated cognitive dysfunction in "primary" dystonia.[143] It concludes that dystonic patients experience multidomain cognitive difficulties: motor and non-motor speed, global cognition, language, executive functioning, learning/memory, visuospatial/construction, and simple/complex attention.[143] There was heterogeneity in the data regarding motor/non-motor speed and learning/memory. Patients with inherited etiology had worse performance than those with acquired dystonia.[143]

The most frequently reported impairment in sleep is excessive daytime sleepiness, insomnia, and fatigue.[91, 96, 144] Less often, PwD may also present a REM behavior disorder and restless leg syndrome.[145] A 2016 systematic review concluded that at least half of patients with focal cranial dystonia had sleep disturbances.[146] Sleep problems may lead to higher anxiety, depression, and pain levels.[144, 146] Even after treatment with botulinum toxin, reduced sleep quality

persists.[146] This further highlights the need to evaluate and treat dystonia's NMS even after the motor treatment is underway.

QoL is a significant but often neglected issue in dystonia, and most studies primarily evaluate CD or blepharospasm. A 2019 meta-analysis on people with idiopathic dystonia revealed that patients had worse QoL than healthy controls.[147] A 2021 observational prospective multicenter case-control study with CD patients found that pain, measured through the DNMSQuest and the TWSTRS, and emotional well-being had the most impact on QoL. [12]

3.6 Dystonia's motor treatment overview

Dystonia treatment is complex, as it is usually done in an individualized manner. Dystonias' classification helps to decide between different types of available treatments (Figure 2).

The pharmacological treatment[50, 148] usually comprises:

i. Levodopa, which should be tested, especially in children and young adults, as some dystonias are dopa-responsive. The most common dopa-responsive dystonias are the DYT-*GCH1* and DYT-*TH,* which display a remarkable improvement. Doses are typically between 1-10 mg/kg/day.
ii. Anticholinergics such as biperiden and trihexyphenidyl. Their shortcoming is the possibility of sedation, hallucination, and cognitive alterations, effects usually diminished with slow titration.
iii. Benzodiazepines.
iv. Baclofen, a GABAergic agonist that may also improve inherited and spastic dystonias. There are oral tablets and an intrathecal formulation.
v. Tetrabenazine, a monoamine uptake inhibitor, is beneficial in tardive dyskinesias/dystonias.

vi. Clozapine, an atypical antipsychotic, may be used in refractory cases, especially in tardive dyskinesias/dystonias. It is essential to highlight that dopamine antagonists are usually avoided because of the risk of tardive dyskinesia/dystonia and/or a possible worsening of dystonia.

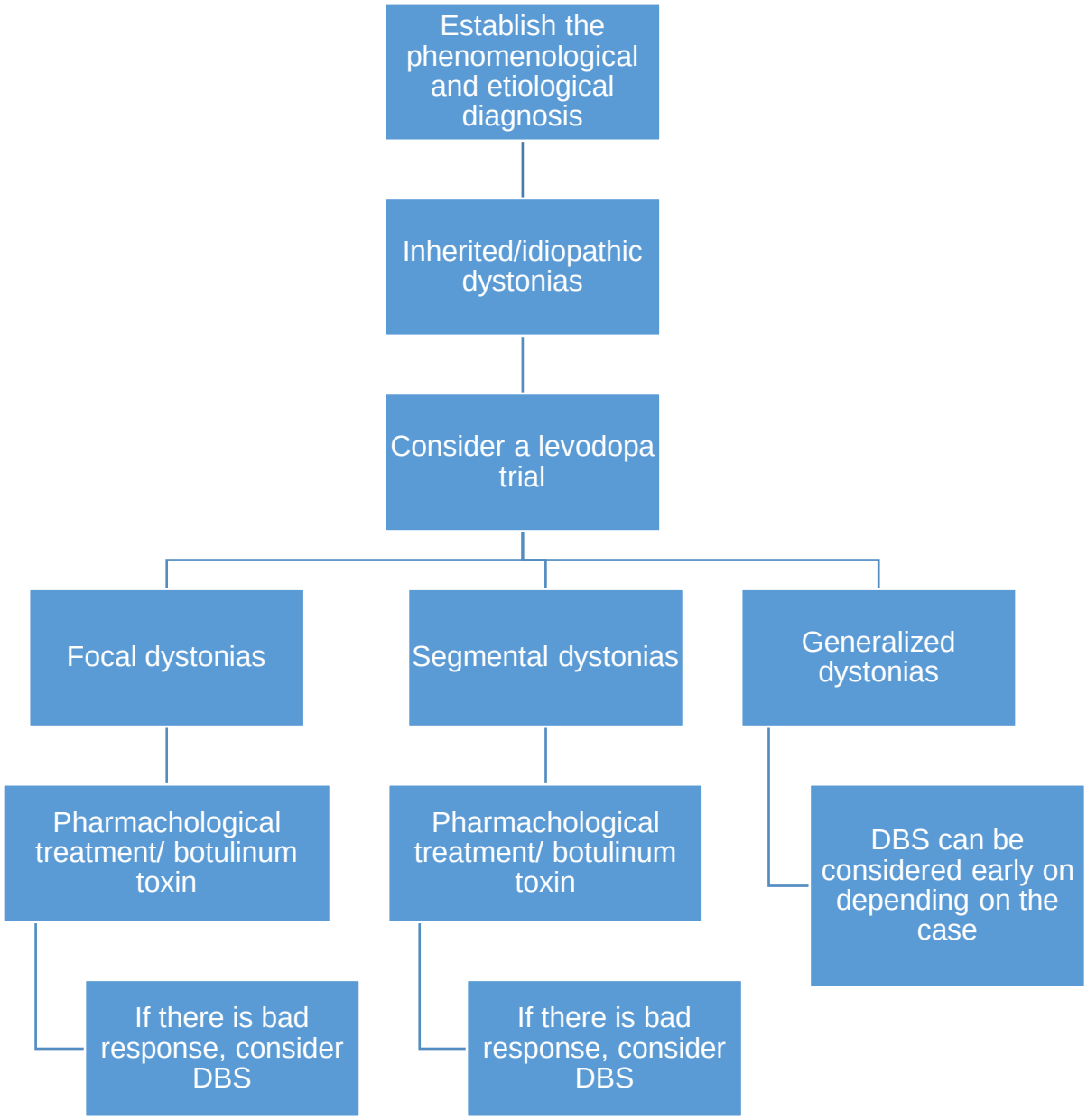
Botulinum toxin is the first-line treatment for most dystonias and, more importantly, in the focal and segmental subtypes. [123, 149-151]. It acts by inhibiting acetylcholine's release in the presynaptic neuron, thus leading to temporary chemical denervation and, therefore, muscular weakness.[152]

Common side effects are dysphagia, weakness, eyelid ptosis, xerostomia, and other autonomic effects,[152] depending on multiple factors, including the application technique and dose. Antibodies can be generated against the toxin leading to a primary or secondary failure to treatment. This is called immunological resistance to the toxin. Secondary failure is characterized by a first and positive response after the toxin's application, with following sessions presenting a shorter duration of the toxin's effect or even a decrease in its response.[152]

Moreover, botulinum toxin currently treats many pain syndromes, including chronic migraines.[153] The neurotoxin is transported to the dorsal root ganglia and to the spinal dorsal horn terminal, affecting nociceptive processing.[154]

Surgical treatment is crucial in the treatment of many PwD. Surgery is usually selected when there is a suboptimal response to the pharmacological.[148, 155] Ablative procedures like thalamotomy and pallidotomy are still used with good responses. Nowadays, magnetic resonance-guided focused ultrasound (MRgFUS) may expand the use of ablative procedures in dystonia.[156]

Figure 2 — Motor treatment rationale in inherited/idiopathic dystonias. In both focal and segmental dystonias, the pharmacological treatment, including botulinum toxin, is usually the first treatment step. Deep brain stimulation (DBS) is generally used if there is an inadequate/insufficient response or if the response lessens with time. Depending on a case-by-case analysis, DBS may be considered early in generalized dystonia.



Both unilateral and bilateral pallidotomy are still good treatment options in patients with dystonia. A retrospective study evaluating 89 patients with “primary” dystonias found that patients with unilateral pallidotomy (n = 20) had an improvement of 51.8% in the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS). In comparison, the 69 patients with bilateral pallidotomy improved by 74%.[157] Nevertheless, bilateral pallidotomy induced parkinsonism, dysarthria, and dysphagia in 9 patients, and the study does not recommend the bilateral procedure. A recent systematic review of bilateral pallidotomy found that this procedure is effective and relatively safe for some dystonias, especially in status dystonicus.[158] They revealed that in 100 patients, 79% of patients had a clinically relevant improvement (> 20%). Eight patients had permanent adverse effects, including dysarthria, dysphonia, aphonia, and dysphagia.

A Japanese group frequently uses thalamotomy for focal hand dystonias,[159] including task-specific dystonias like writer’s cramp, musician’s dystonias, and other occupational dystonias. They have published many case reports and a retrospective analysis of 171 patients with dystonias, in which 80.2% had a good response, and 17.5% showed a partial response.[159]

A paper comparing thalamotomy and pallidotomy for refractory dystonia reveals that pallidotomy had a significantly better improvement. It highlights that patients with acquired dystonias showed more modest results.[160]

DBS is the most used surgical option. The initially described target for stimulation was the thalamus’ *ventralis intermedius nucleus* (VIM); currently, this area is used more for treating tremors, including dystonic tremors.[78] The classic target for dystonia is the GPi,[69-73, 78, 161] although there are currently many studies showcasing equal motor improvement after STN DBS.[75-77]

DBS indication depends on many factors, like the patient’s age, comorbidities, neuropsychological and neuropsychiatric scenario, the duration of the disease, type of dystonia, and past pharmacological and surgical treatments.[78, 162]

The pharmacological treatment for generalized dystonias is usually insufficient to achieve all the desired responses.[78, 148, 163] DBS is indicated if the

patient becomes refractory to the pharmacological treatment for focal or segmental dystonias.[78] In these patients, botulinum toxin and the above-mentioned medications are always the first choice and majorly bring excellent and beneficial results.[148]

It is advised to suggest the DBS procedure before the appearance of fixed deformities (i.e., structural deformation due to sustained abnormal posture),[78, 162] because they do not show resolution after DBS. The longer the disease duration, there are more substantial risks of deformities like cervical myelopathies in people with CD. A shorter disease time and a younger candidate are good outcome predictors.[162, 164]

DBS usually has a good motor outcome in inherited or idiopathic isolated generalized or segmental dystonias, with long-term motor improvement ranging from 42% to 80% in the BFMDRS.[71, 73, 78, 165]

Patients with idiopathic isolated focal dystonia are usually indicated for surgery if refractory to pharmacological treatment. They also expected to have good motor improvement after DBS.[78] In open-label studies, motor improvement can achieve up to 70%.[78] In Meige syndrome (in which there is a combination of blepharospasm and oromandibular dystonia), many studies with GPi or STN DBS have favorable results.[166-169]

PwD who have acquired forms may have very different motor outcomes after DBS, with tardive dyskinesia/dystonia having the most remarkable improvement[74, 78] and other forms, like cerebral palsy, generally not as good.[78, 170]

There is no evidence to delay surgical treatment if it is indicated.[78] There is no specific cut-off for how severe the dystonia should be before surgery.[162] It should be discussed with the patient aspects of the surgical procedure to ensure that the patient knows what is expected to improve and what usually does not. The evaluation of risk and benefit should always be shared with the patient. The most troublesome symptom for the patient should be known, and the team and the patient should discuss whether DBS may be able to improve it.

Screening for psychiatric comorbidities like depression and anxiety is essential.[78] Suicidal ideation should also be evaluated.[162] If the patient is not psychiatrically stable, the surgical procedure should be postponed until stability is achieved. Patients should also be previously assessed for cognitive impairment.

Therefore, the surgical selection is always individualized[78] and should bear in mind the patient's expectations, social background, and support network. Especially in the initial time after the surgical procedure, the patients are frequently evaluated in the DBS center, and reasonable access to it is essential.

Furthermore, another essential part of dystonia treatment is physiotherapy.[171, 172] The combination of botulinum toxin and physiotherapy is superior to the isolated toxin application.[172, 173] Unfortunately, rehabilitation, in general, has few studies in dystonias when compared to other movement disorders like PD.[172, 174] Rehabilitation data is scarce, unfortunately, and should be the focus of more studies in PwD.

3.7 Non-motor symptoms' treatment

There is no systematic review or meta-analysis for NMS treatment in PwD. Usually, the studies evaluate the established motor treatment effects on NMS. Also, it is essential to emphasize that there is no specific guideline for NMS treatment in dystonia. In clinical practice, neurologists usually use the usual pharmacological and non-pharmacological treatment options for most of the NMS.

Even now, most botulinum toxin and DBS studies focus mainly on motor outcomes.[5] Studies that describe NMS outcomes are scarce and primarily evaluate patients with CD.[5, 20, 175] There is a single systematic review of DBS's effect on NMS,[5] which recommends a systematic evaluation of the NMS before and after treatment to improve patients' clinical management and QoL.[5]

A DBS study recruited children with acquired dystonias (mainly patients with cerebral palsy),[176] a subgroup of patients that does not show an optimal motor response to DBS, usually around 25%.[78] The main conclusion in this paper was that, although many patients do not have good motor improvement when measured by the BFMDRS, some may have meaningful responses in other child and family-centered goals like pain and comfort, school attendance, seating tolerance, access to assistive technology and care burden.[176] This, again, highlights the importance of NMS and other outcomes besides motor improvement.

An interesting study tried to evaluate botulinum toxin treatment's effect on NMS in CD.[175] The toxin significantly improved pain and psychiatric symptoms but not any sleep disorders. However, the motor improvement did not correlate to the NMS changes after treatment.[175] It is essential to point out that pain was assessed only by the pain subitem of the TWSTRS.

Another study with CD patients treated with botulinum toxin injections found an improvement in pain between the first and last injection cycle in 76.5% of patients. The presence of pain seemed to increase disability and the symptoms' severity.[177]

Regarding DBS's pain effect, GPi-DBS reduces short- and long-term pain independent of dystonia's etiology, though CD and isolated generalized dystonias have more evidence than craniocervical and acquired forms.[5] For instance, a study found that dystonic pain was present in 45% of a group of 140 children with different forms of dystonia. DBS reduced pain in 90% of them and all etiological groups, including cerebral palsy.[178]

Pain outcome seems to be dissociated from the motor one, with pain improving even if the motor symptoms are refractory to DBS.[5, 148, 179] This indicates that the basal ganglia's dysfunctional circuits may lead to an altered nociception processing, which contributes to the generation/maintenance of pain.[180]

Our group published the only study that evaluated sensory thresholds using QST in patients with DBS. DBS did not affect the abnormal sensory thresholds in

PwD.[14] A more robust evaluation of DBS's outcome for NMS and CP was done in eleven patients with inherited/idiopathic generalized dystonia.[11] By applying the NMS scale for PD patients, we observed that 47.5% displayed an improvement in a one-year follow-up. Three patients improved their CP after DBS, while four still had CP. CP scales like the Brief Pain Inventory short-form (BPI), the Neuropathic Pain Symptoms Inventory (NPSI), and the short-form McGill Pain Questionnaire significantly improved after DBS.[11]

In terms of psychiatric results, GPi-DBS is a safe treatment option in idiopathic/inherited dystonia, when patients have stable psychiatric symptoms.[5] Only preliminary reports show aggravating symptoms of depression or anxiety after DBS, more frequently in tardive dystonia, DYT-*SGCE*, and cerebral palsy. A routine follow-up of these patients is needed.[5]

GPi-DBS does not seem to have a great impact on cognition after surgery. However, studies vary on how cognition is assessed, and there might be an influence on medication management.[5] Very few reports are found regarding sleep disturbances and autonomic issues; thus, their response to DBS is still unclear.[5]

QoL improved after botulinum toxin and DBS.[147, 181] It is important to emphasize that PwD significantly improved QoL after GPi-DBS[69, 161, 163, 165, 182-184], probably due to motor and NMS improvement.[5] STN-DBS is safe, and its motor and QoL results are comparable to GPi-DBS.[75, 185]

As GPi-DBS, the most common DBS target, does not have many well-established reports, other DBS targets and the ablative procedures have even less evidence to be further discussed.

3.8 Scale development

The literature review for my Master's Degree dissertation[44] highlighted a research gap: there was no significant effort to describe and classify CP in dystonia. Therefore, it was decided to develop the Dystonia Pain Classification

System (Dystonia-PCS). This section aims to run through key elements for scale development and how to evaluate the scales' psychometric properties.

The main items of the psychometric analysis are the scale validity and reliability.

3.8.1 Validity

Validity is a term that means how accurate is the representation of specific information.[186] There are many ways to access validity:[187]

- Construct validity: how well a test determines the concept it was designed to assess.[188] Establishing the overall validity of a method, a scale, or a test is crucial. There are two main types of construct validity:
  - Convergent construct validity: it measures the extent to which a measure or a scale that is expected to be related/similar is related (i.e., Dystonia-PCS intends to be a type of pain scale and is compared to other pain scales). This is why when doing a psychometric analysis study, one usually administers different previously validated scales.[187]
  - Divergent or discriminant construct validity measures the extent to which a construct or a scale that is expected to be unrelated to another construct is unrelated/distinct.[187]
- Criterion validity: how the scale precisely measures the concrete outcome it was created to measure or how much the outcomes of a test approximate the results of another test.[187] To evaluate criterion validity, the correlation between the results of your measurement and the results of the criterion measurement is calculated. If there is a high correlation, it indicates that your test is measuring what it indeed intends to measure.
- Content validity: how a test/scale covers all relevant parts of the construct it aims to measure.[187] It requires an evaluation from a panel of experts. The committee must classify each component of the scale as “essential,” “useful,

but not essential," or "not necessary" for measuring the construct. The higher the agreement among panelists that an item is essential, the higher that item's level of content validity is. It is, therefore, subjective.

- Face validity: how the test content appears to be suitable to what it means to measure.[186, 187] It is a subjective assessment and the weakest form of validity, but it can be helpful in the initial stages of the scale's development. Researchers ask experts and/or potential participants if the components of the scale are relevant, useful, and appropriate to what is being measured.

3.8.2 Reliability

Reliability is defined as the extent to which measurements can be replicated, or in other words, to what extent a test or scale is consistent concerning one or more sources of inconsistency (i.e. when considering the selection of raters or considering temporal aspects such as the day and time of testing).[189] The reliability coefficients assess the consistency of a measurement scale and quantify the instrument's precision (accuracy on repeated trials) and, therefore, the trustworthiness of the scores.[186] Evidence of reliability was provided using two tests: internal consistency and retest reliability.

3.8.2.1 Internal consistency

Internal consistency is a measure of scale reliability.[186] It measures how closely related a set of items are as a group. There are many different ways to measure internal consistency:[187]

- The intraclass correlation coefficient (ICC) measures the degree of correlation and agreement between measurements.[189] It is used for quantitative/numeric variables (continuous or discrete variables). In addition, it is used as a reliability index in test-retest, intra-rater, and inter-rater reliability analyses. It may be classified as follows: poor correlation (< 0.4), reasonable

correlation (0.4–0.6), good correlation (0.6–0.75), and excellent correlation (0.75–1.0).[190]

- Fleiss-Kappa: is used for categorical/qualitative variables (i.e., characteristics that can't be quantifiable). However, they can be nominal (describing a name, label, or category without natural order or ordinal – a variable whose values are defined by an order relation between the different types). Kappa ranges from -1 to 1, with negative values showing no concordance, or low (0–0.2), considerable (0.2–0.4), moderate (0.4–0.6), substantial (0.6–0.8), and excellent concordance (> 0.8).
- Pearson's r: It is used for quantitative/numeric variables and measures the direction and strength of the relationship between two variables. It works with a linear relationship between the two variables. It is used to evaluate the reliability of instruments and the validity of evidence (predictive and concurrent). Pearson's r ranges from -1 to 1, with 1 representing perfect correlation.
- Spearman's ρ: It is a nonparametric rank correlation measure and ranges from -1 to 1. It works with linear and monotonic relationships between the variables.
- Cronbach's alpha varies between 0 to 1 and provides an overall assessment of a measure's reliability. If the scale's items are entirely independent of one another, then α = 0. The higher the α coefficient, the more the elements share covariance and, thus, possibly measure the same underlying concept. The α coefficient is acceptable if it is between 0.65 and 0.8 (or higher); α < 0.5 are usually suboptimal.[191]

3.8.2.2 Test-retest reliability

It is helpful to apply the same test at two different intervals to assess reliability. In that way, one can establish inter- and intra-rater reliability:

- Inter-rater reliability reflects the variation between two or more raters who measure the same subjects.[189]

- Intra-rater reliability demonstrates the variation of data measured by one rater across two or more trials.[189]

4 MATERIAL AND METHODS

4.1 Type of study

This was a cross-sectional, multicenter study to develop a CP classification system in Dystonia with a test-retest reliability step. This thesis originated from an article that has been published in Movement Disorders. [192] The Journal agreed to give copyright clearance to reproduce the article's content for this thesis (APPENDIX A and APPENDIX B).

4.2 Place

Consecutive dystonic patients, either with or without CP, were recruited for this study. Eight different centers were invited to participate, and after online meetings, five were selected based on recruitment potential. Patients' evaluation and data collection were done in Movement Disorders and/or Functional Neurosurgery Outpatient Clinics in 5 different centers in Brazil:

1) *Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP)*;

2) *Hospital Geral de Fortaleza (HGF)*, Ceara State;

3) *Hospital das Clínicas da Universidade Federal de Minas Gerais* (UFMG), Minas Gerais State;

4) *Instituto de Ensino Superior do Piaui*, Piaui State;

5) *Escola Paulista de Medicina – Universidade Federal de São Paulo* (UNIFESP), Sao Paulo State.

4.3 Duration of the study

This study started in July 2020, with PwD being recruited until July 2022. Data analysis and manuscript elaboration were finished in November 2022.

4.4 Ethics

The Institutional Review Board approved this study (*Comissão de Ética para Análise de Projetos de Pesquisa, CAPPesq, do HC-FMUSP*, nº 4.093.866, APPENDIX C). It was also approved by the Department of Neurology board of *Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo*. All patients gave written informed consent (APPENDIX E) to participate in the study after understanding the information provided in the informed consent paper according to the current Brazilian legislation for research in human beings (*Resolução do Conselho Nacional de Ética em Pesquisa, CONEP 196/96*).

The local institutional review boards approved the study protocol at all five different centers in Brazil:

1) *Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo*, Sao Paulo State (protocol number #31832920.2.1001.0068), whose principal investigator (PI) was Dr. Clarice Listik, MD, MSc, with help from Dr. Fabricio Vale, MD and Dr. Jorge Dornellys da Silva Lapa, MD.
2) *Hospital Geral de Fortaleza*, Ceara State (protocol number #43188521.4.1001.5040), whose PI was Dr. Flávia de Paiva Santos Rolim, MD, MSc, with help from Professor Dr. Fernanda Martins Mais Carvalho, MD, Ph.D. and Dr. Pedro Rubens Araújo Carvalho, MD.
3) *Hospital das Clínicas da Universidade Federal de Minas Gerais*, Minas Gerais State (protocol number #31832920.2.2003.5149), whose PI was Professor Dr. Sarah Teixeira Camargos, MD, Ph.D., with help from Dr. Mauro Cunningham, MD.
4) *Instituto de Ensino Superior do Piaui*, Piaui State (protocol number #31832920.2.2009.5210), whose PI was Dr. Denise Maria Meneses Cury Portela, MD, MSc, with help from Natália Rebeca Alves de Araújo.

5) *Escola Paulista de Medicina – Universidade Federal de São Paulo*, Sao Paulo State (protocol number #40427220.0.1001.5505), whose PI was Professor Dr. Henrique Ballalai Ferraz, MD, MSc, Ph.D., with help from Dr. Graziele Costa Santos, MD.

4.5 Patients

According to international guidelines, adult patients with the diagnosis of inherited or idiopathic dystonia of any distribution were included.[1] Both patients with and without CP were recruited. Patients were excluded if they were cognitively impaired, could not communicate (anarthria), or did not consent to participate.

Two 90-minute online training sessions were conducted to ascertain homogeneity in patient assessment and data collection using the Research Electronic Data Capture (REDCap) data management platform.[193]

4.6 Patients' clinical and functional status assessments

4.6.1 Clinical, neurological, and motor evaluation

PwD were clinically examined and were classified using international dystonia guidelines[1] by neurologists specialized in movement disorders. At baseline, general information concerning dystonia and clinical history were gathered.

For the motor assessment, we used both the motor (0–120) and disability subscores (0-29) of the BFMDRS, with higher scores indicating worse dystonia and worse disability.

The BFMDRS is a motor scale specific for dystonia and has two subscores:[194] the motor subscores, which comprise nine items (i.e., eyes; mouth;

speech and swallowing, neck, left and right arm, trunk, and left and right leg), each with a severity factor that is multiplied by a provoking factor; and the disability subscore comprised of seven items (speech, handwriting, feeding, eating/swallowing, hygiene, dressing, and walking).

4.6.2 Quality of life and other non-motor symptoms evaluation

Non-motor scales were applied, including mood, quality of life (QoL), and pain scales. For mood and QoL assessments, the Hospital Anxiety and Depression Scale (HADS) and the European Quality of Life 5 Dimensions 3 Level Version, also known as EuroQol-5D-3L (EQ), were applied.

The HADS scale has 14 questions (half concerning depressive symptoms and the other half anxiety symptoms), each scoring 0-3 points, totaling 0–21.[195]

As for the EQ scale, it comprises five items to measure QoL: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each item, the patient can choose the response that better describes their reality (for example, no problem/some problems/unable to or no pain/moderate pain/ extreme pain) rated from 0–2[196]. Also, there is a Visual Analogue Scale (VAS) rated from 0–100 to choose what better describes their *current* health, with 100 being the best and 0 the worst[196].

4.6.3 Pain assessment scales

The questionnaires used for pain assessment in this study were also used in previous studies from the Department of Pain:[11, 14, 24, 197]

1. The BPI short-form provides two subscores: pain severity score, which is the mean of questions 3–6, based on items about pain intensity, each ranging between 0–10; and the pain interference score in daily

activities, calculated as the mean of questions 9A to 9G, each ranging from 0–10.[198, 199]

2. The DN4 assesses a possible neuropathic component of the pain. Scores of ≥ 4 are positive. The scale estimates the sensory pain quality (items 1–7). The last three items (8–10) are based on clinical examination (i.e., hypoesthesia and allodynia).[200, 201]

4.6.4 Development of the Dystonia Pain Classification System

4.6.4.1 The Dystonia Pain Classification System (Dystonia-PCS)

The Dystonia Pain Classification System (Dystonia-PCS) is a rater-based scale (Figure 3) that was developed similarly to the previously published Parkinson's Disease Pain Classification System (PD-PCS).[129]

This classification system was designed according to recommended and established steps for scale development.[202] Due to the absence of CP scales in dystonia, we analyzed the existing classifications of CP in other movement disorders like PD.[25-28, 129] Item generation was based on the advice and experience of movement disorders and pain specialists. Meetings with both specialist teams made the basis for the questionnaire development, reducing the item pool by rejecting poor or redundant items. Dystonia-PCS's main aim was to (i) ascertain whether pain can be related to dystonia (directly related or aggravated by dystonia) or unrelated to it; (ii) to develop a severity score for each type of pain in which pain's intensity, frequency, and impact on daily living are quantified. In addition, the scale aimed to be practical and quantify the experience of PwD's pain. The severity score was established with the pain intensity (rating from 0 to 10), multiplied by its frequency and the impact on daily living (each using a 3-point Likert score, Figure 3). The scores can range from 0 to 90 for each pain type, using the same rationale from the PD-PCS.[25, 26, 129]

A Likert score or scale is a psychometric scale used in research to assess participants' opinions or attitudes toward a topic.[203] It can vary from two items

responses to seven or even nine options. Here we opted for 3-items in order to keep the scale more practical, using the same rationale from the PD-PCS. [129]

Dystonia-PCS's Step 1 is to ascertain whether the patient has CP. Step 2 establishes the relation between pain and dystonia, resulting in three different types of pain: pain directly related to dystonia, pain aggravated by dystonia, and pain unrelated to dystonia. The terminology 'undetermined' is used if the pain cannot be classified as such. The final step (Step 3) calculates a score in which pain intensity (scored 0-10), pain frequency (1-3), and pain impact on daily living (1-3) are multiplied, resulting in a final score ranging from 0-90 (Figure 3). The 'undetermined' pain was also scored as described in Step 3. The Brazilian Portuguese version is seen in Figure 4.

Questions A and B1 try to ascertain if the pain began with the motor symptoms or right after it (A); or if the pain began before the motor symptoms and worsened after it (B1). To illustrate how the scale is applied, here are some examples of possible answers to the scale:

1. Patient without Chronic pain: In this scenario, in Step 1, the patient, at the moment of the assessment, will not have pain lasting longer than three months; therefore, he is classified as having an absence of chronic pain.
2. Patient with chronic pain directly related to dystonia: In this scenario, in Step 1, the patient, at the moment of the assessment, will have pain lasting longer than three months; therefore, he is classified as having chronic pain and moves forward to Step 2. In Step Two, for example, he may have pain that began right after the motor symptoms of dystonia (answering affirmatively to question A). The patient's pain can somewhat improve after the continuous treatment with botulinum toxin (answering affirmative to question B3, but the answers to the other questions were negative). However, the patient still had chronic pain during the assessment (response to Step 1 was affirmative). He is therefore classified as having chronic pain directly related to dystonia. The patient then proceeds to Step 3.

3. Patient with chronic pain aggravated by dystonia: In this scenario, in Step Two, for example, he had chronic pain before the beginning of dystonia (answering negatively to question A). The patient's pain worsens after the motor symptoms of dystonia (responding affirmatively to question B1). However, the patient still had chronic pain during the assessment (response to Step 1 was affirmative). He is therefore classified as having chronic pain aggravated by dystonia. The patient then proceeds to Step 3.
4. Patient with chronic pain unrelated to dystonia: In this scenario, in Step Two, for example, he had chronic pain before the beginning of dystonia (answering negatively to question A). The patient's pain is unaffected by motor symptoms or dystonia's treatment (answering negatively to all questions B1-B3). The patient still had chronic pain at the time of the assessment (response to Step 1 was affirmative). He is therefore classified as having chronic pain unrelated to dystonia. The patient then proceeds to Step 3.

Raters assessed patients' pain with the classification tool in a standardized way. The scale was first applied to a small sample of 8 patients to establish face validity, obtain patients' opinions on the questions asked, and to estimate the approximate time to fill it in (i.e., the target was that trained personnel could apply it in 5 minutes). The final scale received input at national and international movement disorders and pain conferences, where the tool's methodology was presented. After this evaluation, the Dystonia-PCS were consolidated, and all centers started recruiting patients and collecting data to validate the tool´s psychometric properties and quality.[202]

Patients were asked whether they had pain (hereafter described as main chronic pain) most of the days lasting more than three months (i.e., CP) and to indicate the spatial location of their main CP on an electronic mannequin. In addition, patients were allowed to show whether they had a second type of pain (henceforth named secondary chronic pain) and were instructed to indicate its location on a second mannequin template. Differentiation and reporting on the

presence of a second pain syndrome was left to each patient´s discretion. Thus, the main and secondary CP were evaluated by the Dystonia-PCS.

Figure 3 — The Dystonia Pain Classification System (Dystonia-PCS). Step 1 is to ascertain whether the patient has chronic pain. Step 2 establishes the relation between pain and dystonia, resulting in three different types of pain: pain directly related to dystonia, pain aggravated by dystonia, and pain unrelated to dystonia. If the pain cannot be classified in Step 2, it is called undetermined pain. The final step is calculating a score in which pain intensity (0-10), pain frequency (1-3), and pain impact on daily living (1-3) are multiplied, resulting in a final score ranging from 0-90. The undetermined pain can also be scored.

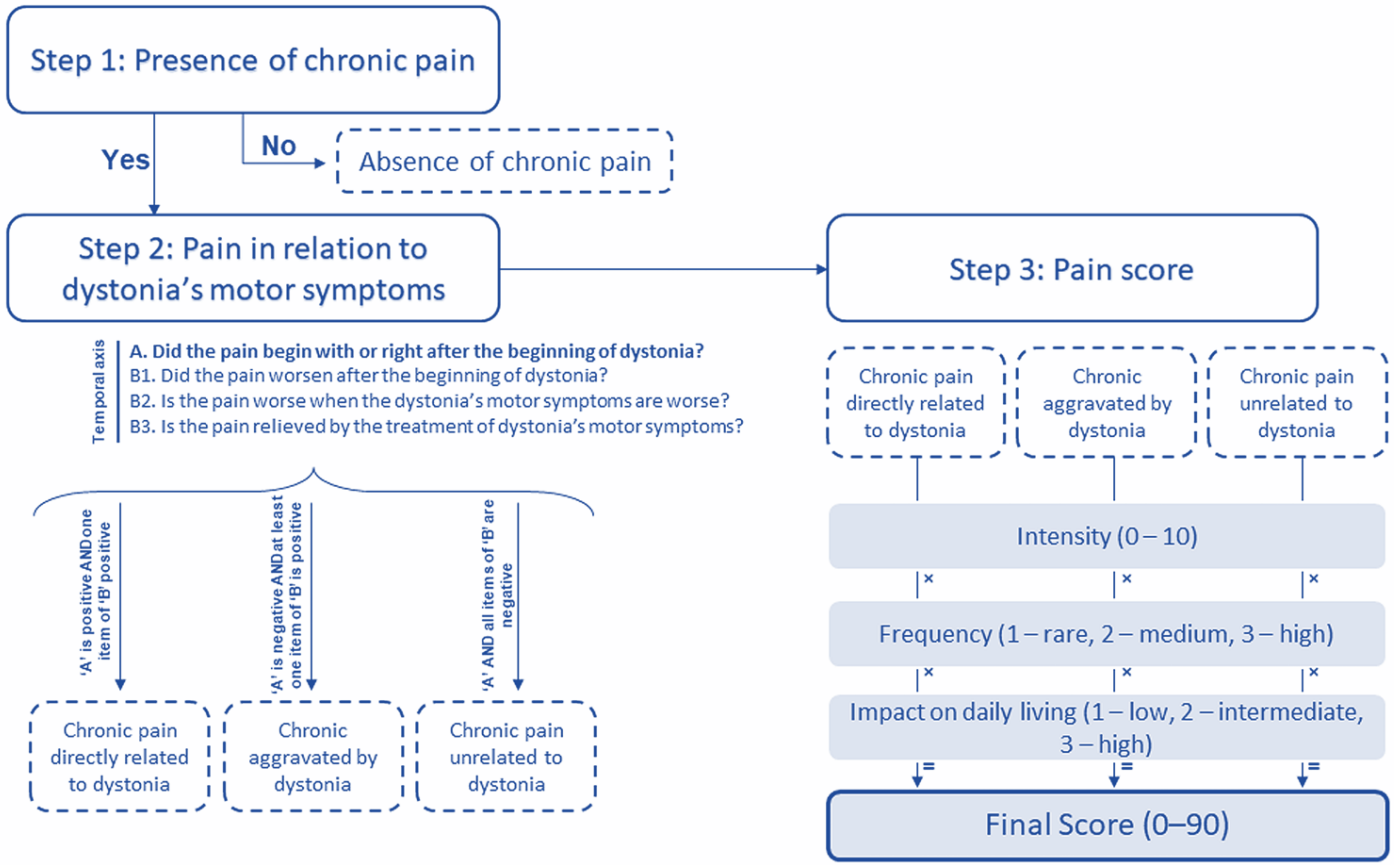
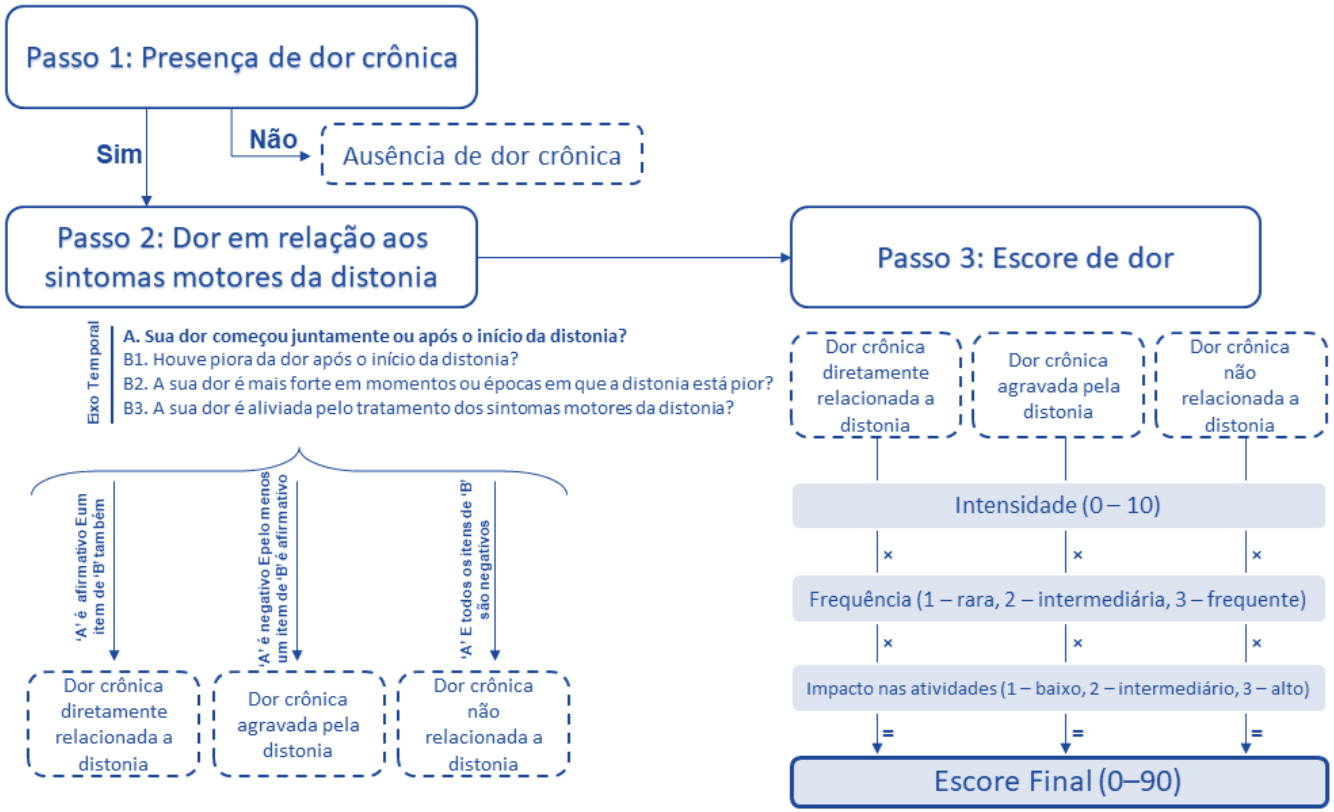


Figure 4 — Brazilian Portuguese version of the Dystonia Pain Classification System (Dystonia-PCS).



4.6.4.2 Re-test reliability step on short and long-term

Eight researchers were responsible for patient assessment by the Dystonia-PCS and participated in the intra- and inter-rater reliability assessments. Some patients were reassessed by the same rater to determine intra-rater reliability or by a second blinded rater to determine inter-rater reliability.

Additionally, a sample of CP patients was reassessed six months and two years after the initial interview to assess the long-term sensitivity to change of the Dystonia-PCS. In these later instances, assessments were made by a structured video conference, and information on the presence of CP, quality of life (EQ's VAS), pain intensity (BPI pain intensity items 3-6), and the Dystonia-PCS data were gathered.

4.7 Statistical Analysis

4.7.1 Sample Size

Using the 10-times-item estimation rule[204] and based on the items of the Dystonia-PCS, 70 PwD with CP would be needed. The sample size was adjusted to around 80 to account for lost data. A subsample of 30 CP patients was considered enough to calculate reliability.

4.7.2 Data analyses

Data from the single centers were collected and integrated for analysis. Data were expressed as mean ± standard deviation (s.d.) (min–max).

All statistical calculations were performed using the Statistical Package for the Social Sciences software (SPSS, version 28.0.0; SPSS Inc., Chicago, IL, USA), and statistical significance was set at $p < 0.05$.

A comparison between patients with and without CP for demographic data (Table 3) and motor and non-motor scales (Table 4) was made using the Chi-squared test for categorical and Mann-Whitney for continuous variables. Mann-Whitney and Qui-square tests were also used to compare the CP questionnaires and Dystonia-PCS scores from patients with and without specific motor treatments for dystonia (e.g., botulinum toxin, oral drugs, deep brain stimulation-DBS – Table 7, Table 8 and Table 9). In addition, patients with longer and shorter motor symptoms duration based on percentiles (75 and 25) were also compared concerning general CP questionnaires and scales scores and Dystonia-PCS scores (Table 10).[20]

Population distribution analyses were performed based on normality (Kolmogorov-Sminirov, Shapiro-Wilk tests) and other elements such as skewness and floor and ceiling effects.

The scale's psychometric properties were evaluated through its validity and reliability.[189, 205] Face validity determines the test accuracy, and in our study, it was established by the expert panel described before.[206] In addition, criterion validity analyzes whether a test correlates to another gold standard measure (i.e., how a new pain classification associates with an established pain scale)[205], and construct validity evaluates the relationship with other scales (e.g., HADS and EQ).

Reliability refers to test consistency.[189, 205] Reliability tests were performed to investigate raters and the internal consistency of the scale's data. In addition, correlation tests were applied using the Spearman rank test to identify the scale's validity with motor and non-motor elements.

A correlation was also observed in patients evaluated after a second evaluation to observe the changes of the Dystonia-PCS with the scales mentioned above.

Finally, multigroup testing (such as the ones differentiating scale subgroups) was made using the Kruskal-Wallis test. Pain types with less than 5% of the total

number of patients with CP (i.e., less than four patients) underwent descriptive but not further inferential analyses.

4.7.3 Validation Analysis

Scale validation was run through the following items:

Acceptability was assessed by evaluating the proportion of missing data, the distribution of scores, skewness, and the presence of floor and ceiling effects. Floor and ceiling effects were calculated as the proportion of cases with Dystonia-PCS scores below 5% or above 95% of total scores, respectively, in patients with pain evaluated by the BPI.

Internal consistency was evaluated by the intraclass correlation coefficient (ICC). Usually, coefficient values above 0.6 show acceptable reliability.[189]

Intra-rater and interrater reliability were assessed by the Fleiss-Kappa scores for dichotomous variables or ICC for continuous variables. The test-retest procedure makes it possible to compare the results of the same rater twice or the results of two different raters.[189, 205] The main and secondary CP were used for this analysis to increase the sample size. Again, reliable scores were considered with statistics above 0.6.[189]

Criterion validity was explored by correlating Dystonia-PCS scores with BPI scores using the Spearman correlation technique. Convergent and divergent construct validity were estimated through the Kruskal-Wallis test by correlating the presence and intensity of each type of pain as set by the Dystonia-PCS with the BFMDRS, BPI, DN4, HADS, and the EQ. Known-group validity was evaluated by comparing the scores from the four pain types (subgroups of the Dystonia-PCS) according to QoL and disease specificities.

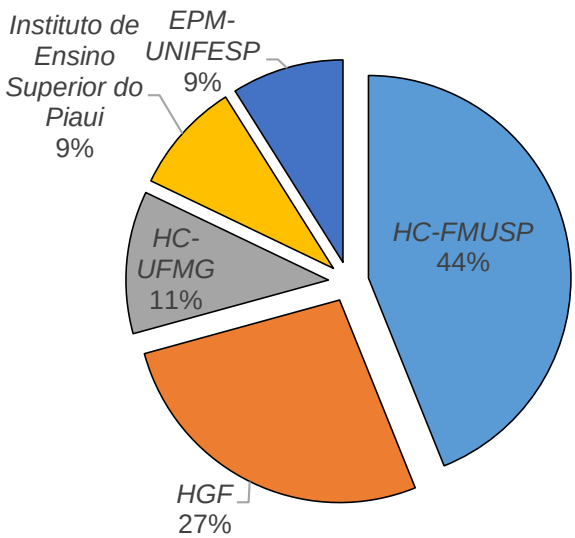
5 RESULTS

5.1 Sample description

5.1.1 Overall clinical features

A total of 123 patients (55.3% female, n = 68) were recruited in five different centers in Brazil (Figure 5). Forty-four percent of patients were recruited from *Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo (HC-FMUSP)*, *Sao Paulo* State, Brazil; 27% from *Hospital Geral de Fortaleza (HGF)*, *Ceara* State, Brazil; 11.4% from *Hospital das Clínicas da Universidade Federal de Minas Gerais (HC-UFMG)*, *Minas Gerais* State, Brazil; 9% from *Instituto de Ensino Superior do Piaui*, *Piaui* State, Brazil; and, 9% from *Escola Paulista de Medicina – Universidade Federal de São Paulo (EPM-UNIFESP)*, *Sao Paulo* State, Brazil). The main characteristics of patients are shown in Table 3.

Figure 5 — Centers that recruited patients.



Forty-two patients had focal dystonia - Figure 6 (i.e., 34% of patients, with n = 8 patients having blepharospasm; n = 3, Meige Syndrome; n = 27 CD, and n = 4 having focal hand dystonia), 39 patients had segmental dystonia (31.7% of patients), 34 had generalized dystonia (27.6%, with n = 26 having leg involvement and 8 without it), 7 multifocal types of dystonia (5.7%) and 1 having hemidystonia (Figure 7). In addition, all patients had idiopathic or hereditary dystonia. Patients were 51.31 ± 15.81 (18–85) years old. Dystonia's duration was 19.98 ± 13.34 (0.01–59) years. BFM motor and disability scores were 19.84 ± 20.32 (0.5–106) and 4.95 ± 5.57 (0–29), respectively. Verbal fluency (animals) was 14.10 ± 5.86 (0–32). HADS anxiety, depression, and total scores were 7.34 ± 5.13 (0–21), 6.32 ± 5.00 (0–19), and 13.66 ± 9.32 (0–40), respectively.

Figure 6 — Focal dystonias.

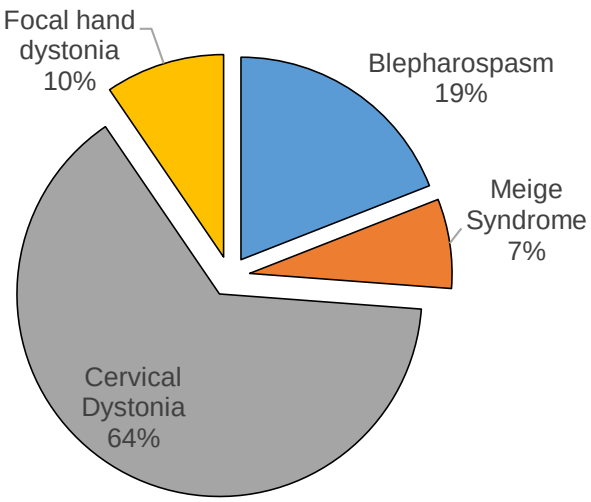


Figure 7 — Patients' dystonia distribution.

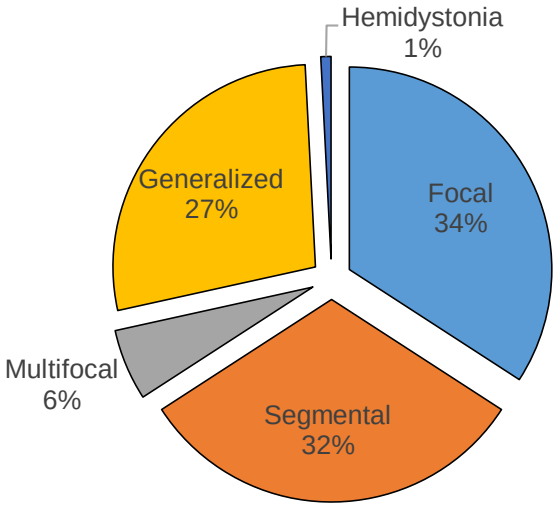


Table 3 — Patients demographics.

	No chronic pain n=42	Chronic pain n=81	P
Female sex	18 (14.6%)	50 (40.7%)	0.046
Age (years)	49.57 ± 17.04 (18-82)	52.22 ± 15.17 (21-85)	0.517
Right handedness	38 (30.9%)	71 (57.7%)	0.802
Employed	24 (19.5%)	42 (34.1%)	0.577
Dystonia duration (years)	18.91 ± 13.15 (0-44)	20.54 ± 13.48 (1-59)	0.539
Dystonia distribution			
Focal			
Blepharospasm	5 (4.1%)	3 (2.4%)	0.333
Cervical	7 (5.7%)	20 (16.3%)	0.409
Meige	1 (0.8%)	2 (1.6%)	0.223
Upper limb	3 (2.4%)	1 (0.8%)	0.261
Generalized			
With lower limb	12 (9.8%)	14 (11.4%)	0.408
Without lower limb	2 (1.6%)	6 (4.9%)	0.333
Hemidystonia	0 (0.0%)	1 (0.8%)	-
Segmental	10 (8.1%)	29 (23.5%)	0.434
Multifocal	2 (1.6%)	5 (4.1%)	0.321
Dystonia's treatment			
Biperiden	6 (4.9%)	10 (8.1%)	0.762
Clonazepam	4 (3.3%)	11 (8.9%)	0.514
Trihexyphenidyl	0 (0.0%)	7 (5.7%)	0.050
Diazepam	0 (0.0%)	1 (1.6%)	0.305
Alprazolam	0 (0.0%)	1 (0.8%)	0.470
Botulinum Toxin application			
Yes	34 (27.6%)	68 (55.3%)	0.453
No	8 (6.5%)	13 (10.6%)	0.397
Deep Brain Stimulation			
Yes	7 (5.9%)	8 (6.8%)	0.378
No	34 (28.8%)	69 (58.5%)	0.454

Data presented as n (%) or mean ± standard deviation (min-max). Categorical variables were compared by the Chi-squared test and the continuous ones by the Mann-Whitney test.

5.1.2 Chronic pain data

CP was present in 65.8% of patients (n = 81). Patients with and without CP had similar clinical, demographic (i.e., age), and dystonic characteristics (i.e., dystonia´s duration, distribution, and treatment), only diverging in treatment with trihexyphenidyl and proportion of female sex (Table 3). Notably, the distribution of dystonia did not affect the Dystonia-PCS score (p = 0.371).

In addition, groups did not differ regarding the motor and QoL scores (Table 4). However, depression and anxiety were significantly worse in patients with CP, and semantic verbal fluency was less affected in these patients.

CP patients had a pain intensity of 4.84 ± 2.50 (0–9.25) and pain interference of 4.26 ± 3.22 (0–10). Twenty-four patients (30.37%) had neuropathic pain (DN4 positive). Thirty-eight patients with CP, i.e., 46.91%, had more than one site of pain (n = 25 had two different CPs, n = 7 had three CPs, n = 3 had four CPs, and n = 3 had more than four different pains).

For the main CP (Table 5), 67 were directly related to dystonia (82.72%), 7 were aggravated by dystonia (8.64%), 6 were non-related to dystonia (7.41%), and 1 was undetermined (1.24%). The main CP (Figure 8 and Figure 9) was most frequently localized in the cervical region (n = 52; 64.2%), followed by cephalalgia and low back pain (n = 5, 6.2% each), shoulder pain, knee pain (n = 4, 4.9%), and other types of pain (upper limb, n = 3; lower limb, n = 2; interscapular pain, n = 1; dorsal pain n = 1; maxilar pain n = 1; eye pain, n = 1; foot pain, n = 1, and, hip pain, n = 1). %). In 67 patients, there was information regarding if CP was located where dystonia was and in 58 (86.57%) it was, meaning that 9 patients had their CP away from the dystonia location (Table 6).

Thirty-eight patients had another CP that was classified (Table 5). In the secondary CP (Figure 10), 22 were directly related to dystonia (57.90%), 10 were aggravated by dystonia (26.32%), 4 were non-related to dystonia (10.53%), and 2 were undetermined (5.26%). This pain was low back pain in 14 patients (36.8%), cephalalgia in 8 patients (21.1%), and cervical pain in 7 patients (18.4%). Other

types of pain were lower limb pain (n = 2), shoulder pain (n = 2), upper limb pain (n = 2), low back pain (n = 1), foot pain (n = 1), and chest pain (n = 1).

We have further analyzed whether oral pharmacological treatment, botulinum toxin, or DBS influenced pain and Dystonia-PCS scores (Table 7, Table 8 and Table 9). There were no differences between treated and non-treated groups. We compared pain and Dystonia-PCS scores of patients with shorter (p25th) and longer (p75th) dystonia's duration (Table 10). There were also no differences.

Table 4 — Patients' motor and non-motor scales.

	No chronic pain n=42	Chronic pain n=81	P
EQ			
EQ-VAS	72.93 ± 23.50 (0-100)	65.31 ± 25.81 (0-100)	0.131
Mobility			
No problems	29 (24.0%)	43 (35.5%)	0.445
Some problems	11 (9.1%)	35(28.9%)	0.431
A lot of problems	2 (1.7%)	1 (0.8%)	0.223
Looking after myself			
No problems	33 (27.5%)	56 (46.7%)	0.450
Some problems	8 (6.7%)	19 (15.8%)	0.409
A lot of problems	1 (0.8%)	3 (2.5%)	0.261
Doing usual activities			
No problems	27 (22.5%)	35 (29.2%)	0.440
Some problems	11 (9.2%)	40 (33.3%)	0.434
A lot of problems	4 (3.3%)	3 (2.5%)	0.321
Having pain or discomfort			
No problems	33 (27.3%)	8 (6.6%)	0.426
Some problems	9 (7.4%)	54 (44.6%)	0.441
A lot of problems	0 (0.0%)	17 (14.0%)	0.439
Feeling worried, sad, or unhappy			
No problems	26 (21.5%)	28 (23.1%)	0.436
Some problems	13 (10.7%)	37 (30.6%)	0.433
A lot of problems	3 (2.5%)	14 (11.6%)	0.386
BFMDRS			
Motor subscore	21.74 ± 22.80 (0.5-84)	18.89 ± 19.03 (2-106)	0.751
Disability subscore	5.10 ± 6.26 (0-22)	5.24 ± 4.95 (0-29)	0.508
Verbal fluency	12.90 ± 5.69 (0-28)	14.71 ± 5.89 (0-32)	0.024
HADS			
Anxiety subscore	4.95 ± 4.32 (0-18)	8.62 ± 5.11 (0-21)	<0.001
Depression subscore	4.33 ± 3.75 (0-15)	7.38 ± 5.27 (0-19)	0.002
Total score	9.29 ± 7.26 (0-31)	16.00 ± 9.50 (0-40)	<0.001

Data presented as n (%) or mean ± standard deviation (min-max). Categorical variables were compared by the Chi-squared test and the continuous ones by Mann-Whitney test. N= number of patients. EQ: EuroQol-5D-3L; EQ-VAS: EuroQol's Visual Analogue Scale; BFMDRS: Burke-Fahn-Marsden Dystonia Rating Scale; HADS: Hospital Anxiety and Depression Scale.

Table 5 — Chronic pain characteristics.

	Main chronic pain n=81	Secondary chronic pain n=38
Pain location		
Headache	5 (6.2%)	8 (21.1%)
Cervical	52 (64.2%)	7 (18.4%)
Posterior thoracic pain	1 (1.2%)	1 (2.6%)
Eyes	1 (1.2%)	0 (0.0%)
Feet	1 (1.2%)	1 (2.6%)
Hip	1 (1.2%)	0 (0.0%)
Interscapular	1 (1.2%)	0 (0.0%)
Knee	4 (4.9%)	0 (0.0%)
Low back pain	5 (6.2%)	14 (36.8%)
Lower limb	2 (2.5%)	2 (5.3%)
Jaw pain	1 (1.2%)	0 (0.0%)
Shoulder	4 (4.9%)	2 (5.3%)
Thorax	0 (0.0%)	1 (2.6%)
Upper limb	3 (3.7%)	2 (5.3%)
Pain scales		
Worst pain score	6.42 ± 3.05 (0—10)	-
Least pain score	3.08 ± 2.67 (0—9)	-
Average pain score	5.57 ± 2.46 (0—10)	-
Pain score right now	4.30 ± 3.56 (0—10)	-
BPIs	4.84 ± 2.50 (0—9.25)	-
Average improvement with medication (%)	48.75 ± 36.65 (0—100)	-
General activity	4.89 ± 3.69 (0—10)	-
Mood	4.84 ± 3.99 (0—10)	-
Walking ability	3.53 ± 3.92 (0—10)	-
Normal Work	4.80 ± 4.39 (0—10)	-
Relations with other people	3.69 ± 3.96 (0—10)	-
Sleep	3.95 ± 3.24 (0—10)	-
Enjoyment of life	4.03 ± 4.17 (0—10)	-
BPIi	4.26 ± 3.22 (0—10)	-
DN4	2.43 ± 1.87 (0-7)	-
DN4 positive	24 (30.37%)	-
Dystonia-PCS		
Directly related	67 (82.72%)	22 (57.90%)
Aggravated	7 (8.8%)	10 (26.32%)
Unrelated	6 (7.5%)	4 (10.53%)
Dystonia-PCS score		
Directly related	46.65 ± 24.64 (2—90)	54.50 ± 25.73 (1—90)
Aggravated	47.86 ± 36.38 (7-90)	32.10 ± 19.06 (8—60)
Unrelated	41.50 ± 26.29 (2-90)	61.50 ± 22.11 (36—90)

Data presented as n (%) or mean ± standard deviation (min-max). #Only one patient had a main chronic pain classified as undetermined pain, while two patients had secondary pains classified as such. BPI: Brief Pain Inventory; BPIs: BPI severity subscore; BPIi: BPI interference subscore; DN4: Douleur Neuropathique 4; Dystonia-PCS: Dystonia's pain Classification System.

Figure 8 — The location of chronic pain. (A)-(D) illustrate the pain's location in chronic pain directly related to dystonia, aggravated by dystonia, unrelated to dystonia, and undetermined. The first color scale represents the percentage of pain's location. **(E)** showcases the main chronic pain, regardless of Dystonia-PCS classification, with its own color scale. Pain in the cervical region was the most common location across all types of chronic pain.

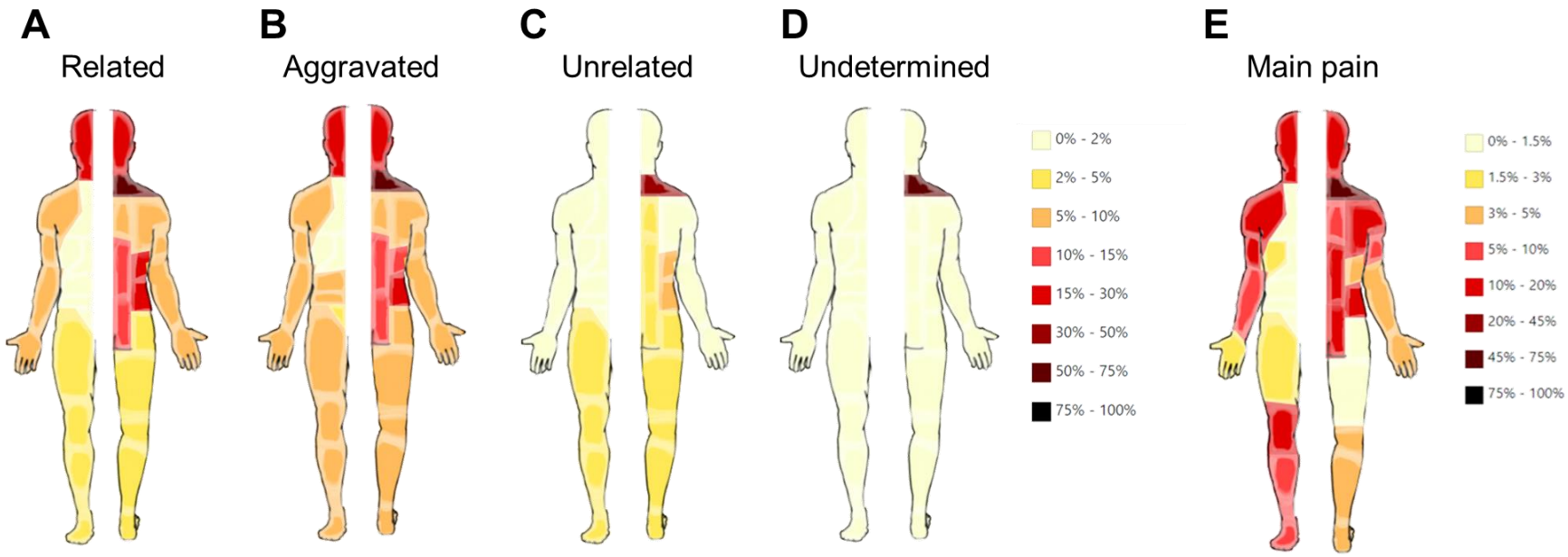


Figure 9 — The location of the main chronic pain.

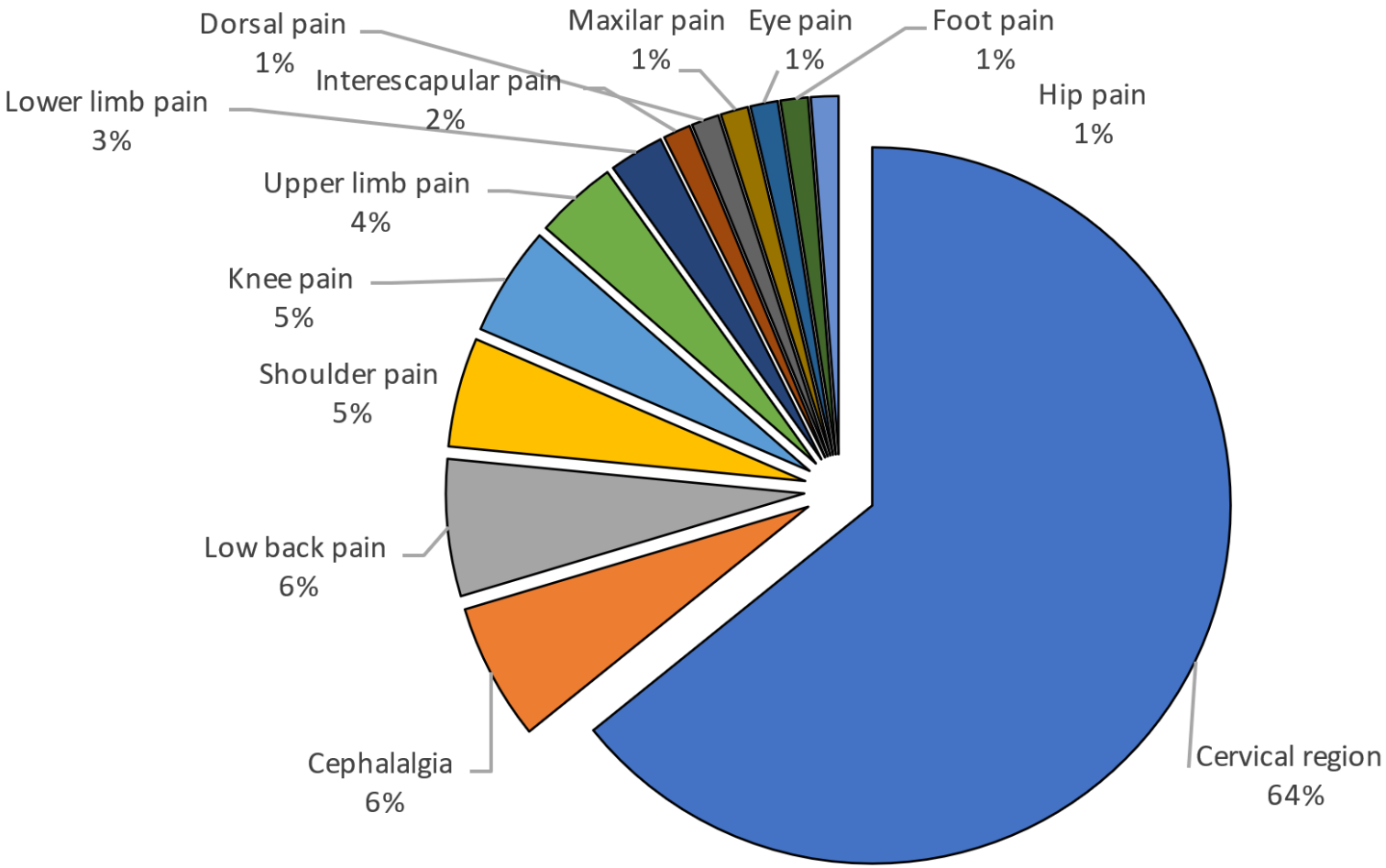


Figure 10 — The location of the secondary chronic pain.

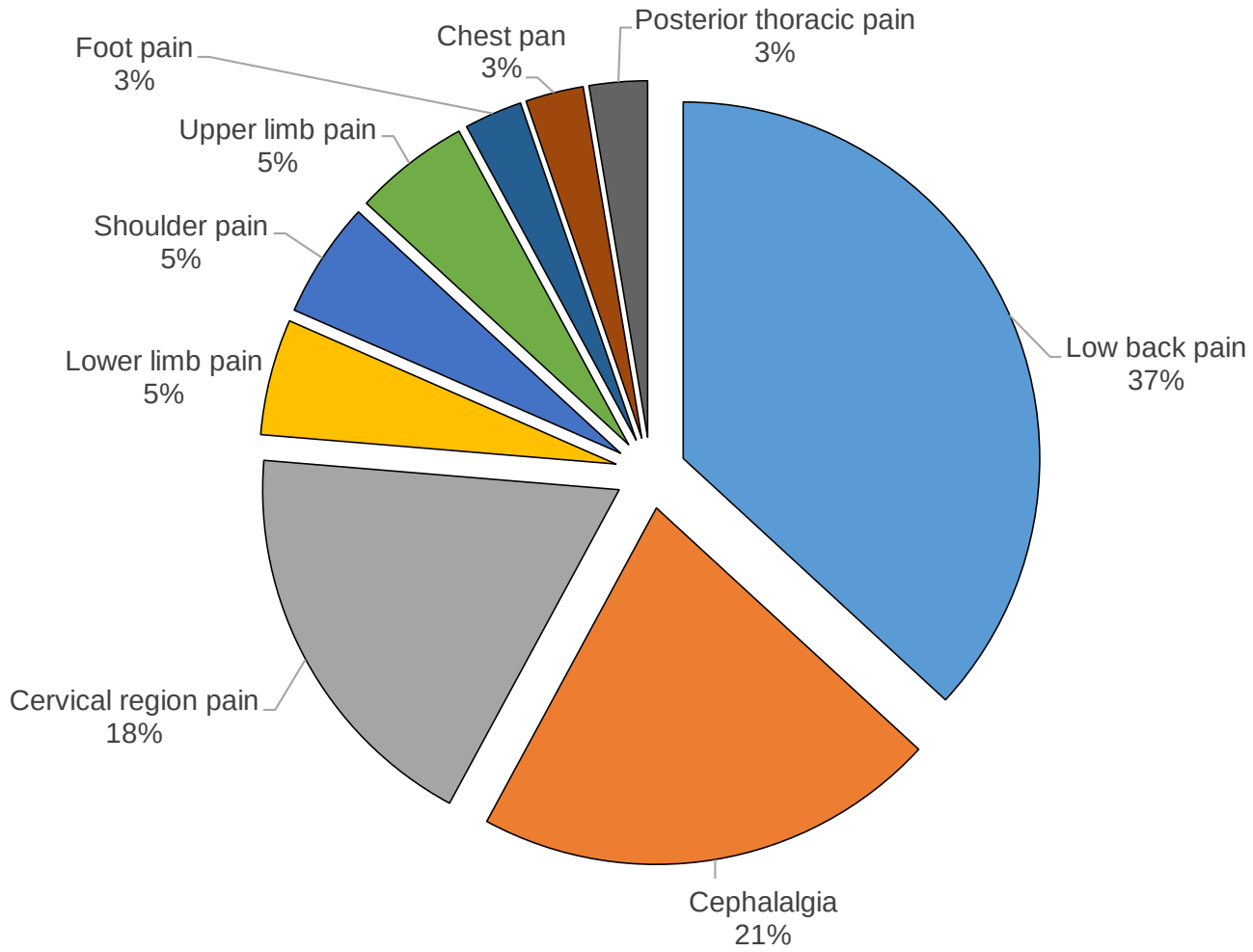


Table 6 — Patients that have their chronic pain away from the dystonia location (n=8).

Distribution		Chronic pain location	Dystonia-PCS
Focal	Blepharospasm	Knee	Unrelated
Segmental		Cervical	Related
Generalized		Cervical	Related
Focal	Meige	Knee	Unrelated
Segmental		Knee	Aggravated
Multifocal		Lower limb	Unrelated
Focal	Blepharospasm	Headache	Aggravated
Focal	Blepharospasm	Cervical	Aggravated
Hemidystonia		Headache	Related

#In 67 patients there was information regarding if CP was located where dystonia was and in 58 (86.57%) it was, meaning that 9 patients had their CP away from the dystonia location. Dystonia-PCS: Dystonia's pain Classification System.

Table 7 — Comparison of chronic pain scales between patients with and without oral pharmacotherapy.

	In pharmacotherapy	No pharmacotherapy	p-value
DN4	2.53 ± 1.94 (0.00–7.00)	2.25 ± 1.78 (0.00–6.00)	0.546
BPIs	4.87 ± 2.63 (0.00–8.75)	4.78 ± 2.26 (0.00–9.25)	0.786
BPIi	4.41 ± 3.36 (0.00–10.00)	4.50 ± 2.96 (0.00–9.29)	0.648
BPI pain right now	4.18 ± 3.65 (0.00–10.00)	4.54 ± 3.44 (0.00–10.00)	0.680
Dystonia-PCS			
Related	42 (82.4%)	25 (83.2%)	0.582
Aggravated	5 (9.8%)	2 (6.6%)	
Unrelated	4 (7.8%)	2 (6.6%)	
Undetermined	0 (0.0%)	1 (3.4%)	
Dystonia-PCS score	46.26 ± 24.69 (2.00–90.00)	45.69 ± 29.34 (4.00–90.00)	0.960

#Mann-Whitney Test and Qui-square were used. BPI: Brief Pain Inventory; BPIs: BPI severity subscore; BPIi: BPI interference subscore; DN4: Douleur Neuropathique 4; Dystonia-PCS: Dystonia's pain Classification System.

Table 8 — Comparison of chronic pain scales between patients with and without botulinum toxin therapy.

	Botulinum toxin	No Botulinum toxin	p-value
DN4	2.60 ± 1.96 (0.00–6.00)	2.37 ± 1.86 (0.00–7.00)	0.619
BPIs	4.87 ± 2.18 (0.00–8.50)	4.83 ± 2.62 (0.00–9.25)	0.990
BPIi	5.37 ± 3.09 (0.00–10.00)	3.88 ± 3.20 (0.00–10.00)	0.096
BPI pain right now	3.68 ± 3.58 (0.00–8.00)	4.51 ± 3.56 (0.00–10.00)	0.419
Dystonia-PCS			
Related	18 (90.0%)	49 (80.3%)	0.471
Aggravated	2 (10.0%)	5 (8.2%)	
Unrelated	0 (0.0%)	6 (9.8%)	
Undetermined	0 (0.0%)	1 (1.6%)	
Dystonia-PCS score	50.80 ± 26.69 (2.00–90.00)	44.47 ± 26.69 (2.00–90.00)	0.338

#Mann-Whitney Test and Qui-square were used. BPI: Brief Pain Inventory; BPIs: BPI severity subscore; BPIi: BPI interference subscore; DN4: Douleur Neuropathique 4; Dystonia-PCS: Dystonia's pain Classification System.

Table 9 — Comparison of chronic pain scales between patients with and without DBS.

	With DBS	Without DBS	p-value
DN4	3.17 ± 1.47 (2.00–5.00)	2.37 ± 1.90 (0.00–7.00)	0.219
BPIs	6.00 ± 1.26 (4.25–7.50)	4.76 ± 2.55 (0.00–9.25)	0.291
BPIi	5.83 ± 3.86 (0.29–10.00)	4.15 ± 3.17 (0.00–10.00)	0.281
BPI pain right now	6.80 ± 2.49 (3.00–10.00)	4.12 ± 3.57 (0.00–10.00)	0.173
Dystonia-PCS			
Related	6 (100.0%)	61 (81.3%)	0.716
Aggravated	0 (0.0%)	7 (9.3%)	
Unrelated	0 (0.0%)	6 (8.0%)	
Undetermined	0 (0.0%)	1 (1.3%)	
Dystonia-PCS score	58.00 ± 20.71 (32.00–90.00)	45.08 ± 26.57 (2.00–90.00)	0.203

[#]Mann-Whitney Test and Qui-square were used. DBS: Deep Brain Stimulation; BPI: Brief Pain Inventory; BPIs: BPI severity subscore; BPIi: BPI interference subscore; DN4: Douleur Neuropathique 4; Dystonia-PCS: Dystonia's pain Classification System.

Table 10 — Comparison of chronic pain scales between patients with shorter disease duration versus longer disease duration.

	p25 (n = 18)	p75 (n = 21)	p-value
Disease time (years)	<= 9	>= 30	-
DN4	2.78 ± 2.24 (0.00–7.00)	2.10 ± 1.38 (0.00–5.00)	0.364
BPIs	4.84 ± 2.61 (0.00–9.00)	4.40 ± 2.05 (1.25–8.25)	0.573
BPIi	4.28 ± 3.30 (0.00–9.00)	4.12 ± 2.80 (0.00–9.71)	0.802
BPI pain right now	4.82 ± 3.56 (0.00–10.00)	3.79 ± 3.39 (0.00–10.00)	0.397
Dystonia-PCS			
Related	17 (53.1%)	17 (50.0%)	
Aggravated	2 (6.3%)	3 (8.8%)	0.574
Unrelated	0 (0.0%)	1 (2.9%)	
Undetermined	0 (0.0%)	1 (2.9%)	
Dystonia-PCS score	41.89 ± 27.33 (4.00–90.00)	52.82 ± 29.14 (6.00–90.00)	0.251

[#]Mann-Whitney Test and Qui-square were used. BPI: Brief Pain Inventory; BPIs: BPI severity subscore; BPIi: BPI interference subscore; DN4: Douleur Neuropathique 4; Dystonia-PCS: Dystonia's pain Classification System.

5.2 Acceptability

The Dystonia-PCS main characteristics are described below (Table 11). The scale has a floor effect of 0 to 2.9% according to the pain subtype and a ceiling effect of 10.5 to 16.7%.

Raters informed that the Dystonia-PCS took 8.12 ± 4.43 (4–15) minutes to be applied.

5.3 Internal consistency

As assessed by ICC, the consistency of pain directly related, aggravated, and unrelated to Dystonia was ICC = 0.925, p = 0.0001.

Table 11 — Acceptability

	Directly related	Aggravated	Unrelated
Skewness	0.180	0.005	0.640
Floor effect (<5%)	2.9%	0%	0%
Ceiling effect (>95%)	10.5%	14.3%	16.7%
Proportion of missing data (chronic pain)	0%	0%	0%
Distribution			
Kolmogorov-Smirnov	P = 0.130	P = 0.200	P = 0.271
Shapiro-Wilk	P = 0.025	P = 0.105	P = 0.189

#Undetermined scale had only one patient, which prevented analysis.##Internal consistency of the scale is ICC = 0.925, p = 0.0001.

5.4 Test-retest reliability

Thirty-seven patients (45.67%) with CP were retested on short-term (Table 12). Twenty-one of them had a second CP. Intra-rater (n = 28 patients) and inter-rater (n = 9 patients) data were obtained using the main and secondary CP (Table 13).

Patients were evaluated by the same researcher (intra-rater reliability) and by a different one (inter-rater reliability). The Dystonia-PCS score showed statistically significant intra-rater (ICC = 0.941) and inter-rater reliability (ICC 0.867). However, due to the small sample size, the undetermined, unrelated, and aggravated pain were excluded from the individual inter and intra-rater reliability analysis, which was only calculated for the directly related pain.

Table 12 — Dystonia-PCS scores were assessed on two occasions.

	Visit #1	Visit #2	Delta	P
Dystonia-PCS				
Directly related CP	32 (86.5%)	31 (83.8%)	-	0.415
Dystonia-PCS score				
Directly related CP score	46.44 ± 23.15 (2-90)	47.48 ± 26.10 (6-90)	-0.45 ± 9.55 (-30-36)	0.877

#number of patients=37. Data presented as n (%) or mean ± standard deviation (min-max). Delta is calculated by subtracting the value in Visit #2 from Visit #1. Continuous variables were compared by the Mann-Whitney test, and the categorical ones by chi-squared. test. Dystonia-PCS: Dystonia's pain Classification System.

Table 13 — Intra-rater and inter-rater reliability.

	Intra-rater (n=45)[#]	P	Inter-rater (n=13)[#]	P
Dystonia-PCS	0.792***	< 0.001	0.207	0.054
Directly related CP	0.773***	< 0.001	0.941**	0.003
Dystonia-PCS score	0.941***	< 0.001	0.867***	< 0.001
Directly related CP score	0.944***	< 0.001	0.868**	0.005

p<0.05, **<0.01, ***<0.001. Kappa scores or intraclass correlation coefficients are shown. Dystonia-PCS: Dystonia's pain Classification System. #n= number of pain assessments (data from the main and secondary chronic pain). The number of patients: intra-rater (28), inter-rater (9).

5.5 Criterion validity and convergent and divergent construct validity

The Dystonia-PCS total score and the Dystonia-PCS score of patients with directly related dystonia CP significantly correlated to both pain scales (BPI subscores and DN4), to the EQ's pain subscore, and both HADS subscores and its total score (Table 14). It shows that the pain classification has an association with other pain scales. The Dystonia-PCS score did not correlate with the BFMDRS.

Table 14 — Correlations between Dystonia-PCS scores and other variables at Visit 1.

	Dystonia-PCS score[##]	P	Dystonia-PCS Related subscore[##]	P
EQ				
EQ-VAS	-0.058	0.614	-0.036	0.777
Mobility	0.229*	0.042	0.226	0.070
Personal care	0.060	0.600	0.024	0.853
Activity	0.189	0.098	0.163	0.199
Pain	0.635***	<0.001	0.597***	<0.001
Anxiety	0.163	0.152	0.241	0.053
BFMDRS				
Motor	-0.007	0.951	-0.042	0.737
Disability	0.166	0.142	0.111	0.376
Verbal fluency	0.034	0.763	-0.018	0.886
HADS				
Anxiety	0.421***	<0.001	0.339**	0.006
Depression	0.300**	0.007	0.276*	0.026
Total	0.407***	<0.001	0.345**	0.005
BPI				
BPIs	0.553***	<0.001	0.499***	<0.001
BPIi	0.609***	<0.001	0.539***	<0.001
Worst pain score	0.609***	<0.001	0.585***	<0.001
Least pain score	0.391***	<0.001	0.288*	0.024
Average pain score	0.450***	<0.001	0.390**	0.002
Pain score right now	0.437***	<0.001	0.429***	<0.001
DN4	0.397***	<0.001	0.364**	0.003

p<0.05, **<0.01, ***<0.001. Spearman's correlation coefficients are shown. EQ: EuroQol-5D-3L; EQ-VAS: EuroQol's Visual Analogue Scale; BFMDRS: Burke-Fahn-Marsden Dystonia Rating Scale; HADS: Hospital Anxiety and Depression Scale; BPI: Brief Pain Inventory; BPIs: BPI severity subscore; BPIi: BPI interference subscore; DN4: Douleur Neuropathique 4; Dystonia-PCS: Dystonia's pain Classification System. N=number of patients.

5.6 Known-group and internal validity

A multinominal logistic regression analysis assessed factors associated with the Dystonia-PCS (Table 15). Patients with CP directly related to dystonia directly correlated to DN4 (coefficient 18.752 ± 1.760, $p < 0.001$) and EQ pain subscores (coefficient 2.830 ± 1.210, $p = 0.023$). However, these patients' scores did not correlate with motor severity or disability.

Table 15 — Multinominal logistic regression analysis.

	Dystonia-PCS directly related score N=60	P
EQ		
EQ-VAS	0.179 ± 0.127	0.166
Mobility	-2.036 ± 6.625	0.012
Personal care	1.962 ± 7.723	0.801
Activity	8.073 ± 6.218	0.201
Pain	23.274 ± 6.929**	0.002
Anxiety	-6.045 ± 5.999	0.166
BFMDRS		
Motor	0.347 ± 0.332	0.303
Disability	-1.555 ± 1.437	0.286
Verbal fluency	0.505 ± 0.472	0.286
HADS		
Anxiety	0.558 ± 0.726	0.447
Depression	1.243 ± 0.889	0.170
BPI		
BPIs	-	
BPIi	-0.127 ± 1.386	0.928
Worst pain	0.097 ± 1.606	0.952
Least pain	-1.200 ± 1.329	0.371
Average pain	1.228 ± 1.697	0.473
Pain right now	2.183 ± 1.186	0.073
DN4	3.639 ± 1.384*	0.012

p<0.05, **<0.01, ***<0.001. EQ: EuroQol-5D-3L; EQ-VAS: EuroQol's Visual Analog Scale; BFMDRS: Burke-Fahn-Marsden Dystonia Rating Scale; HADS: Hospital Anxiety and Depression Scale; BPI: Brief Pain Inventory; BPIs: BPI severity subscore; BPIi: BPI interference subscore; DN4: Douleur Neuropathique 4; Dystonia-PCS: Dystonia's pain Classification System.

5.7 Comparison between the types of pain

We also compared the different pain subtypes, and only the EQ-VAS subscore was different between them, with the directly related pain patients showing lower scores (61.45 ± 26.34, 0–100) *versus* 81.67 ± 17.22 (50–100) for the unrelated pain and 84.29 ± 11.34 (70–100) for the aggravated pain ($p = 0.021$). Therefore, we did not make a post-hoc analysis. Pain location was not different between the subtypes (Figure 8).

5.8 Long-term evaluation of chronic pain

Twenty PwD were evaluated 1.58 ± 0.59 (0.67–2.12) year after their initial evaluation. Sixteen had CP in the first evaluation, while, on the long-term assessment, 12 of them maintained a CP. Three patients did not have CP and maintained that status, while one previously did not and started displaying a low back pain after the first assessment.

The Dystonia-PCS, EQ-VAS, and items 3–6 of the BPI were applied in this long-term re-evaluation (Table 16, Table 17). There was a positive correlation between the 3 BPI's intensity sub-items deltas and the classification delta (worst pain 0.649, $p = 0.002$; least pain 0.454, $p = 0.044$ and average 0.562, $p = 0.010$).

Table 16 — Long-term evaluation of chronic pain.

	ΔLong-term—initial evaluation
BPI	
Worst pain	0.40 ± 4.58 (-10 — 8)
Least pain	-0.75 ± 2.59 (-7 — 5)
Average pain	-0.30 ± 3.11 (-7 — 5)
Pain right now	-1.40 ± 3.58 (-7 — 4)
Dystonia-PCS score	-23.25 ± 29.97 (-90 — 30)
EQ-VAS	-1.95 ± 29.31 (-70 — 50)

#Twenty people with dystonia were re-evaluated (1.58 ± 0.59, 0.67–2.12) year after their initial evaluation. Categorical variables were compared by the Chi-squared test and the continuous ones by Mann-Whitney test. Comparison between the change in the Dystonia-PCS and the change on items 3–6 of the BPI; and EQ-VAS are reported. Dystonia-PCS: Dystonia's pain Classification System; BPI: Brief Pain Inventory; EQ-VAS: EuroQol-5D-3L's Visual Analogue Scale.

Table 17 — Correlation between differential descriptors for long-term chronic pain.

	ΔDystonia-PCS score[#]	**P**
ΔBPI		
ΔWorst pain	0.649	0.002
ΔLeast pain	0.454	0.044
ΔAverage pain	0.562	0.010
ΔPain right now	0.387	0.092
ΔEQ-VAS	-0.413	0.070

#Spearman rank correlation test.ΔDystonia-PCS: Change (re-evaluation – first evaluation) in Dystonia's pain Classification System; ΔBPI: Change (re-evaluation – first evaluation) in Brief Pain Inventory; ΔEQ-VAS: Change (re-evaluation – first evaluation) on EuroQol-5D-3L's Visual Analog Scale.

6 DISCUSSION

The Dystonia-PCS aims to design and validate a pain classification and scoring system for dystonia. It establishes types of CP that are either directly related, unrelated, or aggravated by dystonia and scores the CP's impact. Dystonia-PCS was revealed to be a reliable and quick-to-apply tool.

6.1 Discussing Dystonia-PCS psychometric properties

The Dystonia-PCS was created through established and recommended procedures for scale development.[202] A recent literature review reported no prior classification for CP in dystonia.[21] Therefore, we analyzed existing CP for other movement disorders, especially PD.[25-27, 129] Experts in movement disorders and pain helped generate the scale items, and patients' opinions on the scale were gathered, thus establishing face validity. The final scale was presented at different conferences to gather additional input.

Our internal consistency has an ICC of 0.925, $p < 0.0001$, and our intra-rater (ICC = 0.941) and inter-rater (ICC = 0.867) are classified as excellent results.[190] This means that the Dystonia-PCS is reliable. Furthermore, our scale also had convergent construct validity as it was significantly correlated to both pain scales (BPI and DN4) and the EQ pain subitem. Moreover, in our regression analysis, the directly related dystonia CP correlated with DN4 and EQ pain subitem.

In our study, PwD had moderate pain intensity, most with pain directly related to dystonia (82.72%) and some with pain aggravated by dystonia. Almost 47% of patients with CP had more than one type of pain. While the mixed pain concept has been reported in the general pain field and pain in PD, it has not yet been explored in dystonia.[22, 207] It has long been believed that pain in PwD would be derived from motor over-recruitment and the subsequent activation of muscle, joint, and fascia nociceptors. However, some crucial factors suggest that this

"musculogenic" hypothesis may not entirely explain the higher prevalence of CP in PwD. No direct correlation has been established between dystonia's motor severity and pain intensity.[109] Additionally, efficacious treatments to control dystonic movements may not wholly mitigate pain in PwD, which persists despite improvement of the motor symptoms.[11, 89] The main driving mechanism of dystonia is believed to be the reduction of cortical inhibition, impaired synaptic plasticity, and altered gain in somatosensory processing.[120, 122, 208-211] Our data show that CP's severity and impact did not correlate with dystonia's motor severity or disability. We verified a lack of correlation between the pain score directly related to dystonia and the BFMDRS score, suggesting the presence of different drivers for motor and pain symptoms of the disease. This scenario highlights the need to approach CP in these patients as a primary symptom of dystonia and not simply as a by-product of the motor abnormalities.

6.1.1 Discussing the framework of Dystonia-PCS

One common challenge when assessing pain related to a specific disease is that CP has a baseline prevalence of nearly 20% of the general population worldwide.[212] While determining causality is a philosophical and scientific challenge, the International Classification of Diseases-11 (ICD-11) approach to classifying pain related to neurological diseases uses temporal and aggravation anchors to determine if a pain syndrome is secondary to a neurological disorder.[213] This is the way pain related to multiple sclerosis,[214] PD,[129] and stroke[130] are classified. Pain is a supplementary symptom in patients with neurological disorders. It is classified in temporal relation (or related to symptom aggravation) to the motor/non-pain symptoms of the disease. If, on the one hand, this may be prone to recall bias, especially in longstanding diseases, on the other hand, it is a strategy that reflects the clinical approach, which is based on patient and family history taking. We have opted to use the latter method. While recall bias is very likely to exist, its magnitude is unknown. And based on our data, patients with longer and shorter disease duration presented similar scores in the assessments. This also supports the long-acknowledged lack of correlation

between motor symptoms severity and pain intensity in movement disorders such as PD and dystonia.[5, 9, 11, 14, 44] One important aspect is that the potential bias mentioned above refers to pain classification in step 2. The determination of pain chronicity (step 1) was based on a classic 3-month cut-off which has been extensively validated and is recommended to classify pain as chronic.[215] In step 3, pain severity assessment was based on the present pain, as is commonly used for most pain assessment tools. Besides the potential recall bias mentioned above for step 2 of the Dystonia-PCS, the present study has other limitations. Although the multicenter design allowed us to have a large sample size for a rare disease, only a percentage of patients presented CP. It is known that some PwD may experience pain years before the onset of motor signs of dystonia (e.g., blepharospasm, writer's cramp), though we do not know if it lasts enough to classify it as CP. Therefore, step 2 in those cases may classify the CP as "aggravated by" instead of "directly related to" dystonia. It is not known how many patients experienced it. Still, even in this scenario, steps 1 and 3 were assured and allowed the classification system to perform well in psychometric and validation tests. Overall, Dystonia-PCS classifies this pain that PwD may experience at the location of their dystonia years before the motor symptoms as aggravated by dystonia, showing a relationship between the motor symptom and the pain.

Similar to dementia, where we have primary and secondary dementias, the ICD-11 classifies CP as primary or secondary pain syndromes (e.g., post-surgery (MG 30.2), post-stroke (MG 30.50), or PD-related pains (MG 30.32), including, for instance, chronic secondary musculoskeletal pain associated with PD).[216] By the ICD-11 approach, pain directly related to dystonia would be secondary.[213] And for that, the crucial point is its temporal relationship with the disease (i.e., dystonia) start. We followed this same approach here. Thus, based on the ICD-11 approach and societal recommendations,[216] dystonia-related pain is a secondary pain syndrome classified according to its temporal and symptomatic relationship to the disease.[215, 217, 218] Therefore, we divided the pain according to the time that the motor symptoms appeared because the patient may usually differentiate if the pain began before, during, or after the motor symptoms onset. Also, the patient can infer if the pain is better when the motor

symptoms are better or worse when the motor symptoms are worse, as we saw when we applied the scale. CP in neurological disease may worsen over time due to neurodegeneration or may be influenced by treatment, as shown in PD.[219] And we have followed the same rationale for dystonia. Despite these constraints, to gain further insight and assess to which degree recall bias related to disease duration could significantly affect our results, sensitivity analyses comparing whether patients with short vs. long-standing dystonia showed similar scores in pain questionnaires and Dystonia-PCS.

A general lack of correlation between pain intensity and dystonia severity[5, 9, 12, 109] has been repetitively reported, something also true for other diseases like PD.[219] This may suggest that the neuronal processes responsible for pain initiation and maintenance are probably different than those responsible for motor symptoms burden. In the Dystonia-PCS framework, after determining that pain is chronic, the initiation of motor symptoms of dystonia is used as a time anchor to classify pain as directly related or not to the disease, followed by the determination of pain current intensity and impact. Here too, pain intensity did not correlate with motor symptoms severity. This further supports the view that motor and non-motor symptoms such as pain are likely not only to depend on different mechanisms but also respond differently to treatment and have different prognoses.[11, 14]

6.2 Gaps of knowledge that the Dystonia-PCS fulfills in the current literature

As mentioned, most studies that describe pain in PwD do not distinguish between acute pain and CP. This is a fundamental issue because they are different clinical entities.[220] Pain is an “unpleasant sensory and emotional experience associated with actual or potential tissue damage.”[221] Acute pain can begin from direct trauma or indirectly through biochemical mediators released from damaged or potentially damaged tissue (pressured/ stretched).[222] To stop

acute pain, one should treat the underlying medical cause, disabling the nociceptive signals.[220]

On the other hand, CP has an entirely different facet. It was previously defined as a pain that persists past its normal healing time,[223] lacking the immediate biological warning function of acute pain.[224] CP's definition was improved to a temporal criterion because the "normal healing time" was easy to apply, for instance, in pain after surgery but was less clearly established, for example, in chronic musculoskeletal or neuropathic pain.[224] The current definition is: a pain that lasts or recurs for longer than three months.[225] In CP syndromes, pain can be the sole/leading complaint (chronic primary pain, like fibromyalgia), or it may be secondary to an underlying disease (e.g., chronic cancer-related pain, chronic neuropathic pain).[224]

Therefore, studies in PwD must differentiate between acute and CP. Unfortunately, this cannot be done using pain subitems of QoL scales, the TWSTRS, or VAS. Even using specific NMS scales like the DNMSQuest for CD or the NMS questionnaire for Parkinson's disease, no distinguishing ability is present. The literature mainly uses these scales to evaluate pain in PwD.[4, 20, 67, 89, 99, 123, 125] Specific pain scales were used only in two studies in the literature.[11, 21] One from our group, which evaluated eleven patients with inherited/idiopathic generalized dystonia; more than half of these patients had CP. According to the literature, these patients are not the ones who more frequently describe the pain.[8-10, 20]

The Dystonia-PCS aims to fill this gap as it classifies whether the patient has CP, discerns if CP is related to the dystonia, and furthers scores the intensity, frequency, and impact of the CP on daily living. The Dystonia-PCS fills this knowledge gap by permitting the diagnosis of CP and, thus, being able to separate the CP's causes such as headache,[127, 128] neuropathic pain, low back pain, and so forth. It directly affects patients' pain treatment and, therefore, their QoL. In this sense, it creates a classification framework that can be further increased and detailed, similar to the disease classification systems used for the ICD-11.[213]

6.3 Interesting points that emerged for future studies

Interestingly, in our sample, dystonia's severity and disability were not different when patients with and without CP were compared. Though our study was not powered to evaluate this, it is the first evidence that compared people with and without CP and not just with or without "pain" as other studies before.[109] Another curious data is that patients with and without CP did not differ regarding dystonia's distribution. Therefore, a question arises: what distinguishes patients with and without CP, and what factors influence this distinction? Future studies shall elucidate the reasoning behind this query.

Future endeavors can also focus on differences between the pains directly related, aggravated, or unrelated to dystonia. Our sample showed no difference in pain location between these subtypes, but other studies may assist in understanding if differences are to be present.

The Dystonia-PCS will enable the long-term evaluation of CP in dystonic patients. As a result, we may comprehend the true prevalence of CP across several dystonia subtypes. In addition, we will be able to identify and diagnose pain syndromes and provide more personalized treatment for PwD.

It will also be able to evaluate the established motor treatments for dystonia, like botulinum toxin and DBS' effects on CP.

The scale can be prospectively applied for acquired forms of dystonia. As mentioned before, dystonia is a heterogeneous disease, and it was our option to solely include idiopathic and inherited dystonia in an attempt to maximize our sample's homogeneity.

6.4 Points to consider

This study has some limitations. First, despite having a large sample size, this was not enough to properly quantify the aggravated and unrelated dystonia CP subtypes.

Another one is only one individual in 81 participants was labeled with undetermined pain, i.e., a type of pain that the instrument could not classify. Nevertheless, this did not prevent the pain from being scored (intensity, frequency, and impact on daily living are obtainable). Further studies may help elucidate if it is a unique type of pain or not.

Recall bias may be present in the daily care of patients. Many vital aspects of dystonia could have a recall bias, for instance, where it began, how it spread, when it started, and how long the patient has had dystonia. Response to these is subject to recall bias. Importantly, we do not precisely know its magnitude. It may be small and clinically irrelevant, or it may be gigantic. In addition, it is difficult to determine the time onset of when a recall bias begins to take place, as well as its magnitude. As seen above, many scales choose a time-set, usually lower than the three months to establish pain as chronic.

Based on the ICD-11 approach and societal recommendations, dystonia-related pain is a secondary pain syndrome. It is classified according to its temporal and symptomatic relationship to the disease.[215, 217, 218] Therefore, we chose to divide the pain according to the time that the motor symptoms appeared because, usually, the patient may differentiate if the pain began before, during, or after the motor symptoms onset. Also, the patient can infer if the pain is better when the motor symptoms are better or if it is worse when the motor symptoms are worse, as we saw when we applied the scale. Chronic pain in neurological disease may worsen over time due to neurodegeneration or may be influenced by treatment, as it has been shown in PD.[219] And we have followed the same rationale for dystonia.

Another point to discuss is that we opted to do a CP scale that may be applied to any dystonia type. We agree that a specific CP scale for each type of dystonia would make a scale that is more individualized, with a homogenous sample. Still, it would also make it more challenging to study CP in dystonia owing

to the fact that there are many different types of dystonia. For example, just mentioning focal forms of dystonia, one might have a chronic pain scale for cervical dystonia, blepharospasm, Meige Syndrome, laryngeal dystonia, task-specific dystonia, focal hand dystonia, foot dystonia, and so forth). Not to mention the segmental and generalized isolated forms of dystonia, the combined forms of idiopathic/inherited dystonias, and the acquired dystonias such as tardive dystonia and cerebral palsy. Therefore, we aimed for a more general description of CP in dystonia that can be applied to any dystonia form, and we hope that further studies can also evaluate acquired forms of dystonia with our scale. Therefore, we only chose not to include it in this study in order not to make the sample even more heterogeneous.

Moreover, we could not adequately calculate the analyses for some of the subtypes of pain owing to the sample size. We hope to solve this issue in a prospective, international study that will include more participants and also the acquired forms of dystonias. We hope to start a larger trial to analyze these types of CP more accurately.

As the patients were seen in specialized centers, our sample has an over-representation of primary CD. This may have further influenced our results toward an over-representation of dystonia located in the neck. Despite a sensitivity analysis showing that the psychometric properties of the Dystonia-PCS remained after excluding CD patients, the remaining patients included individuals with segmental, multifocal, and generalized dystonia, who may also have dystonia extended to the cervical region. This means that some rarer types of dystonia, such as laryngeal and all acquired dystonias, may have been under-represented in our validation efforts. It remains to be tested whether the Dystonia-PCS is fully valid in these people.

Additionally, the U.S. Food and Drug Administration and the European Medicines Agency currently recommend that any newly developed patient-facing scales be evaluated not only by experts but also by the patients themselves.[226] While we had rounds of patient meetings and inputs into our classification system, they were limited to a small number of patients and from a limited number of centers. Additionally, the role of patients mainly took place at the beginning of the

project and during its initial design, and not as a long-lasting and perennial counseling and supervision throughout the whole study. We acknowledge that patient participation should have been more intense for a more comprehensive utility and applicability of the classification system.

7 CONCLUSION

We may conclude from this work the Dystonia-PCS is a reliable and quick-to-apply tool with adequate internal consistency and intra and inter-rater reliability. The Dystonia-PCS correlates to established pain scales (e.g., BPI and DN4), and we observed that usual patients and dystonia characteristics did not differentiate people with and without CP.

REFERENCES[1]

1. Albanese A, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013;28(7):863-73.

2. Medina A, et al. The Prevalence of Idiopathic or Inherited Isolated Dystonia: A Systematic Review and Meta-Analysis. Mov Disord Clin Pract. 2022;9(7):860-8.

3. Balint B, et al. Dystonia. Nat Rev Dis Primers. 2018;4(1):25.

4. Eggink H, et al. Motor and non-motor determinants of health-related quality of life in young dystonia patients. Parkinsonism Relat Disord. 2019;58:50-5.

5. Eggink H, et al. Non-motor effects of deep brain stimulation in dystonia: A systematic review. Parkinsonism Relat Disord. 2018;55:26-44.

6. Dahlhamer J, et al. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults - United States, 2016. MMWR Morb Mortal Wkly Rep. 2018;67(36):1001-6.

7. Leao Ferreira KA, et al. Prevalence of chronic pain in a metropolitan area of a developing country: a population-based study. Arq Neuropsiquiatr. 2016;74(12):990-8.

8. Novaretti N, et al. The Prevalence and Correlation of Non-motor Symptoms in Adult Patients with Idiopathic Focal or Segmental Dystonia. Tremor Other Hyperkinet Mov (N Y). 2019;9:596.

9. Kuyper DJ, et al. Nonmotor manifestations of dystonia: a systematic review. Mov Disord. 2011;26(7):1206-17.

10. Stamelou M, et al. The non-motor syndrome of primary dystonia: clinical and pathophysiological implications. Brain. 2012;135(Pt 6):1668-81.

[1] According to: International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical Journals. Can Med Assoc J. 1994 Jan 15; 150(2): 147-54, 159-67.

11. Listik C, et al. Improvement of Non-motor Symptoms and Quality of Life After Deep Brain Stimulation for Refractory Dystonia: A 1-Year Follow-Up. Front Neurol. 2021;12:717239.

12. Klingelhoefer L, et al. Emotional well-being and pain could be a greater determinant of quality of life compared to motor severity in cervical dystonia. J Neural Transm (Vienna). 2021;128(3):305-14.

13. Rosales RL, et al. Pain in cervical dystonia: mechanisms, assessment and treatment. Expert Rev Neurother. 2021;21(10):1125-34.

14. Listik C, et al. Abnormal sensory thresholds of dystonic patients are not affected by deep brain stimulation. Eur J Pain. 2021;25(6):1355-66.

15. Paracka L, et al. Sensory Alterations in Patients with Isolated Idiopathic Dystonia: An Exploratory Quantitative Sensory Testing Analysis. Frontiers in Neurology. 2017;8:553.

16. Suttrup I, et al. Loss of sensory function in patients with idiopathic hand dystonia. Mov Disord. 2011;26(1):107-13.

17. Lobbezoo F, et al. Pain perception in idiopathic cervical dystonia (spasmodic torticollis). Pain. 1996;67(2-3):483-91.

18. Abbruzzese G, Berardelli A. Sensorimotor integration in movement disorders. Mov Disord. 2003;18(3):231-40.

19. Bradley D, et al. Temporal Discrimination Threshold: VBM evidence for an endophenotype in adult onset primary torsion dystonia. Brain. 2009;132(9):2327-35.

20. Camargo CH, Cattai L, Teive HA. Pain Relief in Cervical Dystonia with Botulinum Toxin Treatment. Toxins (Basel). 2015;7(6):2321-35.

21. Amberg A, et al. Unravelling dystonic pain; a mixed methods survey to explore the language of dystonic pain and impact on life. Disabil Rehabil. 2022:1-9.

22. Cury RG, et al. Effects of deep brain stimulation on pain and other nonmotor symptoms in Parkinson disease. Neurology. 2014;83(16):1403-9.

23. Cury RG, et al. Sensory abnormalities and pain in Parkinson disease and its modulation by treatment of motor symptoms. European Journal of Pain (London, England). 2016;20(2):151-65.

24. Cury RG, et al. Subthalamic deep brain stimulation modulates conscious perception of sensory function in Parkinson's disease. Pain. 2016;157(12):2758-65.

25. Chaudhuri KR, et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: Results from an international pilot study. Mov Disord. 2007;22(13):1901-11.

26. Chaudhuri KR, et al. King's Parkinson's disease pain scale, the first scale for pain in PD: An international validation. Mov Disord. 2015;30(12):1623-31.

27. Ford B. Pain in Parkinson's disease. Mov Disord. 2010;25 Suppl 1:S98-103.

28. Wasner G, Deuschl G. Pains in Parkinson disease--many syndromes under one umbrella. Nat Rev Neurol. 2012;8(5):284-94.

29. Timmers ER, et al. Non-motor symptoms and quality of life in dopa-responsive dystonia patients. Parkinsonism Relat Disord. 2017;45:57-62.

30. Page D, Butler A, Jahanshahi M. Quality of life in focal, segmental, and generalized dystonia. Mov Disord. 2007;22(3):341-7.

31. Camargos S, Cardoso F. Understanding dystonia: diagnostic issues and how to overcome them. Arquivos De Neuro-Psiquiatria. 2016;74(11):921-36.

32. Camargo CHF, Teive HAG. Evolution of the concept of dystonia. Arquivos De Neuro-Psiquiatria. 2014;72(7):559-61.

33. Newby RE, et al. A History of Dystonia: Ancient to Modern. Movement Disorders Clinical Practice. 2017;4(4):478-85.

34. Munts AG, Koehler PJ. How psychogenic is dystonia? Views from past to present. Brain. 2010;133(Pt 5):1552-64.

35. Broussolle E, et al. Early Illustrations of Geste Antagoniste in Cervical and Generalized Dystonia. Tremor and Other Hyperkinetic Movements (New York, NY). 2015;5:332.

36. Zeman W, et al. Idiopathic dystonia musculorum deformans. I. The hereditary pattern. Am J Hum Genet. 1959;11(2 Part 1):188-202.

37. Ozelius L, et al. Human gene for torsion dystonia located on chromosome 9q32-q34. Neuron. 1989;2(5):1427-34.

38. Ozelius LJ, et al. The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. Nat Genet. 1997;17(1):40-8.

39. Marras C, et al. Nomenclature of genetic movement disorders: Recommendations of the international Parkinson and movement disorder society task force. Mov Disord. 2016;31(4):436-57.

40. Cooper IS. Dystonia musculorum deformans: natural history and neurosurgical alleviation. J Pediatr. 1969;74(4):585-92.

41. Marsden CD, Sheehy MP. Writer's cramp. Trends Neurosci. 1990;13(4):148-53.

42. Ganos C, Edwards MJ, Bhatia KP. The Phenomenology of Functional (Psychogenic) Dystonia. Movement Disorders Clinical Practice. 2014;1(1):36-44.

43. Albanese A, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013;28(7):863-73.

44. Listik C. Efeitos da estimulação cerebral profunda nos limiares sensitivos e de dor em pacientes distônicos. [Dissertação]. São Paulo: Universidade de São Paulo, Faculdade de Medicina.; 2020.

45. Charlesworth G, Bhatia KP, Wood NW. The genetics of dystonia: new twists in an old tale. Brain. 2013;136(7):2017-37.

46. Defazio G. The epidemiology of primary dystonia: current evidence and perspectives. Eur J Neurol. 2010;17 Suppl 1:9-14.

47. Steeves TD, et al. The prevalence of primary dystonia: a systematic review and meta-analysis. Mov Disord. 2012;27(14):1789-96.

48. Yianni J, Green AL, Aziz TZ. Surgical treatment of dystonia. Int Rev Neurobiol. 2011;98:573-89.

49. Fahn S, Bressman SB, Marsden CD. Classification of dystonia. Adv Neurol. 1998;78:1-10.

50. Albanese A, et al. EFNS guidelines on diagnosis and treatment of primary dystonias. Eur J Neurol. 2011;18(1):5-18.

51. Defazio G, et al. The Italian Dystonia Registry: rationale, design and preliminary findings. Neurol Sci. 2017;38(5):819-25.

52. Carbon M, et al. Tardive Dyskinesia Prevalence in the Period of Second-Generation Antipsychotic Use: A Meta-Analysis. J Clin Psychiatry. 2017;78(3):e264-e78.

53. Rice J, et al. Identification and measurement of dystonia in cerebral palsy. Dev Med Child Neurol. 2017;59(12):1249-55.

54. Dressler D, et al. The epidemiology of dystonia: the Hannover epidemiology study. J Neurol. 2022;269(12):6483-93.

55. Meoni S, Macerollo A, Moro E. Sex differences in movement disorders. Nat Rev Neurol. 2020;16(2):84-96.

56. Ozelius LJ, Lubarr N, Bressman SB. Milestones in dystonia. Mov Disord. 2011;26(6):1106-26.

57. Quartarone A, Hallett M. Emerging concepts in the physiological basis of dystonia. Mov Disord. 2013;28(7):958-67.

58. Nakashima K, et al. Reciprocal inhibition between forearm muscles in patients with writer's cramp and other occupational cramps, symptomatic hemidystonia and hemiparesis due to stroke. Brain. 1989;112 (Pt 3):681-97.

59. Panizza M, et al. H-reflex recovery curve and reciprocal inhibition of H-reflex in different kinds of dystonia. Neurology. 1990;40(5):824-8.

60. Quartarone A, Pisani A. Abnormal plasticity in dystonia: Disruption of synaptic homeostasis. Neurobiol Dis. 2011;42(2):162-70.

61. Morgante F, Klein C. Dystonia. Continuum (Minneap Minn). 2013;19(5 Movement Disorders):1225-41.

62. Kroneberg D, et al. Motor Cortical Plasticity Relates to Symptom Severity and Clinical Benefit From Deep Brain Stimulation in Cervical Dystonia. Neuromodulation. 2017;21(8):735-40.

63. Ramos VFML, Karp BI, Hallett M. Tricks in dystonia: ordering the complexity. J Neurol Neurosurg Psychiatry. 2014;85(9):987-93.

64. Breakefield XO, et al. The pathophysiological basis of dystonias. Nat Rev Neurosci. 2008;9(3):222-34.

65. Lehéricy S, et al. The anatomical basis of dystonia: current view using neuroimaging. Mov Disord. 2013;28(7):944-57.

66. Neychev VK, et al. The basal ganglia and cerebellum interact in the expression of dystonic movement. Brain. 2008;131(Pt 9):2499-509.

67. Klingelhoefer L, et al. Validation of a self-completed Dystonia Non-Motor Symptoms Questionnaire. Ann Clin Transl Neurol. 2019;6(10):2054-65.

68. DeLong MR, Wichmann T. Circuits and circuit disorders of the basal ganglia. Arch Neurol. 2007;64(1):20-4.

69. Vidailhet M, et al. Deep brain stimulation for dystonia. J Neurol Neurosurg Psychiatry. 2013;84(9):1029-42.

70. Vidailhet M, et al. Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. N Engl J Med. 2005;352(5):459-67.

71. Vidailhet M, et al. Bilateral, pallidal, deep-brain stimulation in primary generalised dystonia: a prospective 3 year follow-up study. Lancet Neurol. 2007;6(3):223-9.

72. Kupsch A, et al. Pallidal deep-brain stimulation in primary generalized or segmental dystonia. N Engl J Med. 2006;355(19):1978-90.

73. Volkmann J, et al. Pallidal deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year follow-up of a randomised trial. Lancet Neurol. 2012;11(12):1029-38.

74. Macerollo A, Deuschl G. Deep brain stimulation for tardive syndromes: Systematic review and meta-analysis. J Neurol Sci. 2018;389:55-60.

75. Lin S, et al. Deep brain stimulation of the globus pallidus internus versus the subthalamic nucleus in isolated dystonia. J Neurosurg. 2019:1-12.

76. Tsuboi T, et al. A pooled meta-analysis of GPi and STN deep brain stimulation outcomes for cervical dystonia. J Neurol. 2020;267(5):1278-90.

77. Wu Y-S, et al. Meta-Regression Analysis of the Long-Term Effects of Pallidal and Subthalamic Deep Brain Stimulation for the Treatment of Isolated Dystonia. World Neurosurg. 2019;129:e409-e16.

78. Cury RG, et al. Surgical treatment of dystonia. Expert Review of Neurotherapeutics. 2018;18(6):477-92.

79. Hendrix CM, Vitek JL. Toward a network model of dystonia. Ann N Y Acad Sci. 2012;1265:46-55.

80. Kaji R, Bhatia K, Graybiel AM. Pathogenesis of dystonia: is it of cerebellar or basal ganglia origin? J Neurol Neurosurg Psychiatry. 2018;89(5):488-92.

81. Shakkottai VG, et al. Current Opinions and Areas of Consensus on the Role of the Cerebellum in Dystonia. Cerebellum. 2017;16(2):577-94.

82. Franca C, et al. Effects of cerebellar neuromodulation in movement disorders: A systematic review. Brain Stimul. 2018;11(2):249-60.

83. Kaji R. Direct cerebello-striatal loop in dystonia as a possible new target for deep brain stimulation: A revised view of subcortical pathways involved. Front Neurol. 2022;13:912818.

84. Horisawa S, et al. The striking effects of deep cerebellar stimulation on generalized fixed dystonia: case report. J Neurosurg. 2019;132(3):712-6.

85. Stroud A, Tisch S, Jonker BP. Cerebellar Cortex Stimulation for Acquired Dystonia: A Case Report and Review of Its Role in Modern Surgical Practice. Stereotact Funct Neurosurg. 2022:1-10.

86. Sokal P, et al. Deep anterior cerebellar stimulation reduces symptoms of secondary dystonia in patients with cerebral palsy treated due to spasticity. Clin Neurol Neurosurg. 2015;135:62-8.

87. Defazio G, et al. Blepharospasm 40 years later. Mov Disord. 2017;32(4):498-509.

88. Berman BD, et al. Risk of spread in adult-onset isolated focal dystonia: a prospective international cohort study. J Neurol Neurosurg Psychiatry. 2020;91(3):314-20.

89. Junker J, et al. Quality of life in isolated dystonia: non-motor manifestations matter. J Neurol Neurosurg Psychiatry. 2021;92:622-8.

90. Bailey GA, Martin E, Peall KJ. Cognitive and Neuropsychiatric Impairment in Dystonia. Curr Neurol Neurosci Rep. 2022;22(11):699-708.

91. Timmers ER, et al. Myoclonus-dystonia: Distinctive motor and non-motor phenotype from other dystonia syndromes. Parkinsonism Relat Disord. 2019;69:85-90.

92. Peall KJ, et al. Non-motor symptoms in genetically defined dystonia: Homogenous groups require systematic assessment. Parkinsonism Relat Disord. 2015;21(9):1031-40.

93. Peall KJ, et al. A review of psychiatric co-morbidity described in genetic and immune mediated movement disorders. Neurosci Biobehav Rev. 2017;80:23-35.

94. Martino D, et al. Association and Familial Coaggregation of Idiopathic Dystonia With Psychiatric Outcomes. Mov Disord. 2020;35(12):2270-8.

95. Ceylan D, et al. Evaluation of anxiety and depression scales and quality of LIFE in cervical dystonia patients on botulinum toxin therapy and their relatives. Neurol Sci. 2019;40(4):725-31.

96. Wadon ME, et al. Non-motor phenotypic subgroups in adult-onset idiopathic, isolated, focal cervical dystonia. Brain Behav. 2021;11(8):e2292.

97. Ben-Shlomo Y, et al. What are the determinants of quality of life in people with cervical dystonia? J Neurol Neurosurg Psychiatry. 2002;72(5):608-14.

98. Berardelli I, et al. Clinical course of psychiatric disorders in patients with cervical dystonia. Psychiatry Res. 2015;229(1-2):583-5.

99. da Silva-Junior FP, et al. High prevalence of self-reported non-motor symptoms and lack of correlation with motor severity in adult patients with idiopathic isolated dystonia. Neurol Sci. 2022;43(2):1061-5.

100. Rice ASC, Smith BH, Blyth FM. Pain and the global burden of disease. Pain. 2016;157(4):791-6.

101. Breivik H, et al. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. European Journal of Pain (London, England). 2006;10(4):287-333.

102. Ren K, Dubner R. Descending Control Mechanisms. In: Basbaum A, Bushnell M, editors. Science of Pain. Oxford: Academic Press; 2009. p. 723-62.

103. Charles PD, et al. Cervical dystonia and pain: characteristics and treatment patterns from CD PROBE (Cervical Dystonia Patient Registry for Observation of OnabotulinumtoxinA Efficacy). J Neurol. 2014;261(7):1309-19.

104. Werle RW, et al. The physical, social and emotional aspects are the most affected in the quality of life of the patients with cervical dystonia. Arquivos De Neuro-Psiquiatria. 2014;72(6):405-10.

105. Bartolo M, et al. Assessing and treating pain in movement disorders, amyotrophic lateral sclerosis, severe acquired brain injury, disorders of consciousness, dementia, oncology and neuroinfectivology. Evidence and recommendations from the Italian Consensus Conference on Pain in Neurorehabilitation. Eur J Phys Rehabil Med. 2016;52(6):841-54.

106. Williams L, et al. Epidemiological, clinical and genetic aspects of adult onset isolated focal dystonia in Ireland. Eur J Neurol. 2017;24(1):73-81.

107. Marciniec M, et al. Pain in cervical dystonia and the antinociceptive effects of botulinum toxin: what is currently known? Rev Neurosci. 2019;30(7):771-9.

108. Stacy M. Epidemiology, clinical presentation, and diagnosis of cervical dystonia. Neurol Clin. 2008;26 Suppl 1:23-42.

109. Kutvonen O, Dastidar P, Nurmikko T. Pain in spasmodic torticollis. Pain. 1997;69(3):279-86.

110. Marciniec M, Szczepanska-Szerej A, Rejdak K. Cervical dystonia: factors deteriorating patient satisfaction of long-term treatment with botulinum toxin. Neurol Res. 2020;42(11):987-91.

111. Vilaseca I, et al. Non-motor symptoms in spasmodic dysphonia: A case control-study. Auris Nasus Larynx. 2022;49(1):100-5.

112. Scorr LM, et al. Clinical Features and Evolution of Blepharospasm: A Multicenter International Cohort and Systematic Literature Review. Dystonia. 2022;1.

113. Li S, et al. Non-motor Symptoms in Chinese Patients With Isolated Generalized Dystonia: A Case-Control Study. Front Neurol. 2020;11:209.

114. Gilbert LA, et al. Top 10 Research Themes for Dystonia in Cerebral Palsy: A Community-Driven Research Agenda. Neurology. 2022;99(6):237-45.

115. Tinazzi M, et al. Nociceptive pathway function is normal in cervical dystonia: a study using laser-evoked potentials. J Neurol. 2012;259(10):2060-6.

116. Borsook D, et al. A key role of the basal ganglia in pain and analgesia--insights gained through human functional imaging. Mol Pain. 2010;6:27.

117. Byl N, et al. Sensory dysfunction associated with repetitive strain injuries of tendinitis and focal hand dystonia: a comparative study. J Orthop Sports Phys Ther. 1996;23(4):234-44.

118. Tinazzi M, et al. Sensory functions in dystonia: insights from behavioral studies. Mov Disord. 2009;24(10):1427-36.

119. Scontrini A, et al. Somatosensory temporal discrimination tested in patients receiving botulinum toxin injection for cervical dystonia. Mov Disord. 2011;26(4):742-6.

120. Sadnicka A, et al. Pallidal stimulation for cervical dystonia does not correct abnormal temporal discrimination. Mov Disord. 2013;28(13):1874-7.

121. Klauenberg S, et al. Depression and changed pain perception: hints for a central disinhibition mechanism. Pain. 2008;140(2):332-43.

122. Tinazzi M, et al. Pain in cervical dystonia: Evidence of abnormal inhibitory control. Parkinsonism Relat Disord. 2019;65:252-5.

123. Rodrigues FB, et al. Botulinum toxin type A therapy for cervical dystonia. Cochrane Database Syst Rev. 2020;11(11):CD003633.

124. Consky ES, et al. The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS): assessment of validity and inter-rater reliability. Neurology. 1990;40:445.

125. Chaudhuri KR, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. Mov Disord. 2006;21(7):916-23.

126. Protopapas MG, et al. The complications of scar formation associated with intrathecal pump placement. Arch Phys Med Rehabil. 2007;88(3):389-90.

127. Bezerra ME, Rocha-Filho PA. Headache Attributed to Craniocervical Dystonia - A Little Known Headache. Headache. 2017;57(2):336-43.

128. Eugenio Ramalho Bezerra M, Sampaio Rocha-Filho PA. Headache attributed to craniocervical dystonia: A prospective cohort study. Eur J Pain. 2020;24(8):1484-94.

129. Mylius V, et al. The Parkinson disease pain classification system: results from an international mechanism-based classification approach. Pain. 2021;162(4):1201-10.

130. Barbosa LM, et al. Dissecting central post-stroke pain: a controlled symptom-psychophysical characterization. Brain Commun. 2022;4(3):fcac090.

131. Valerio F, et al. Characterization of pain syndromes in patients with neuromyelitis optica. Eur J Pain. 2020;24(8):1548-68.

132. Han V, et al. Prevalence of non-motor symptoms and their association with quality of life in cervical dystonia. Acta Neurol Scand. 2020;142(6):613-22.

133. Berman BD, et al. Psychiatric associations of adult-onset focal dystonia phenotypes. J Neurol Neurosurg Psychiatry. 2017;88(7):595-602.

134. Bailey GA, et al. Longitudinal analysis of the relationship between motor and psychiatric symptoms in idiopathic dystonia. Eur J Neurol. 2022;29(12):3513-27.

135. Conte A, et al. Non-motor symptoms in patients with adult-onset focal dystonia: Sensory and psychiatric disturbances. Parkinsonism Relat Disord. 2016;22 Suppl 1:S111-4.

136. Worthley A, Simonyan K. Suicidal Ideations and Attempts in Patients With Isolated Dystonia. Neurology. 2021;96(11):e1551-e60.

137. Medina Escobar A, et al. The prevalence of depression in adult onset idiopathic dystonia: Systematic review and metaanalysis. Neurosci Biobehav Rev. 2021;125:221-30.

138. Goodarzi Z, et al. Detecting depression in Parkinson disease: A systematic review and meta-analysis. Neurology. 2016;87(4):426-37.

139. Boeschoten RE, et al. Prevalence of depression and anxiety in Multiple Sclerosis: A systematic review and meta-analysis. J Neurol Sci. 2017;372:331-41.

140. Fiest KM, et al. Depression in epilepsy: a systematic review and meta-analysis. Neurology. 2013;80(6):590-9.

141. Kuring JK, Mathias JL, Ward L. Prevalence of Depression, Anxiety and PTSD in People with Dementia: a Systematic Review and Meta-Analysis. Neuropsychol Rev. 2018;28(4):393-416.

142. Medina Escobar A, Martino D, Goodarzi Z. The prevalence of anxiety in adult-onset isolated dystonia: A systematic review and meta-analysis. Eur J Neurol. 2021;28(12):4238-50.

143. Aita SL, et al. Neuropsychological Functioning in Primary Dystonia: Updated and Expanded Multidomain Meta-Analysis. Mov Disord. 2022;37(7):1483-94.

144. Smit M, et al. Fatigue, Sleep Disturbances, and Their Influence on Quality of Life in Cervical Dystonia Patients. Mov Disord Clin Pract. 2017;4(4):517-23.

145. Ray S, et al. Sleep and other Non-motor Symptoms in Patients with Idiopathic Oromandibular Dystonia and Meige Syndrome: A Questionnaire-based Study. Ann Indian Acad Neurol. 2021;24(3):351-5.

146. Hertenstein E, et al. Sleep in patients with primary dystonia: A systematic review on the state of research and perspectives. Sleep Med Rev. 2016;26:95-107.

147. Girach A, Vinagre Aragon A, Zis P. Quality of life in idiopathic dystonia: a systematic review. J Neurol. 2019;266(12):2897-906.

148. Adam OR, Jankovic J. Treatment of dystonia. Parkinsonism Relat Disord. 2007;13 Suppl 3:S362-8.

149. Jankovic J. An update on new and unique uses of botulinum toxin in movement disorders. Toxicon. 2018;147:84-8.

150. Hallett M, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of movement disorders. Toxicon: Official Journal of the International Society on Toxinology. 2013;67:94-114.

151. Simpson DM, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2016;86(19):1818-26.

152. Smith AG. Pearls and pitfalls in the therapeutic use of botulinum toxin. Semin Neurol. 2004;24(2):165-74.

153. Bendtsen L, et al. Guideline on the use of onabotulinumtoxinA in chronic migraine: a consensus statement from the European Headache Federation. J Headache Pain. 2018;19(1):91.

154. Pellett S, Yaksh TL, Ramachandran R. Current Status and Future Directions of Botulinum Neurotoxins for Targeting Pain Processing. Toxins. 2015;7(11):4519-63.

155. Speelman JD, et al. Deep brain stimulation for dystonia: patient selection and outcomes. Eur J Neurol. 2010;17 Suppl 1:102-6.

156. Horisawa S, et al. Magnetic Resonance-Guided Focused Ultrasound Thalamotomy for Focal Hand Dystonia: A Pilot Study. Mov Disord. 2021;36(8):1955-9.

157. Horisawa S, et al. Safety and efficacy of unilateral and bilateral pallidotomy for primary dystonia. Ann Clin Transl Neurol. 2021;8(4):857-65.

158. Centen LM, et al. Bilateral Pallidotomy for Dystonia: A Systematic Review. Mov Disord. 2021;36(3):547-57.

159. Horisawa S, et al. Safety and long-term efficacy of ventro-oral thalamotomy for focal hand dystonia: A retrospective study of 171 patients. Neurology. 2019;92(4):e371-e7.

160. Yoshor D, et al. Comparison of thalamotomy and pallidotomy for the treatment of dystonia. Neurosurgery. 2001;48(4):818-24; discussion 24-6.

161. Mueller J, et al. Pallidal deep brain stimulation improves quality of life in segmental and generalized dystonia: results from a prospective, randomized sham-controlled trial. Mov Disord. 2008;23(1):131-4.

162. Bronte-Stewart H, et al. Inclusion and exclusion criteria for DBS in dystonia. Mov Disord. 2011;26 Suppl 1:S5-16.

163. Moro E, Gross RE, Krauss JK. What's new in surgical treatment for dystonia? Mov Disord. 2013;28(7):1013-20.

164. Moro E, et al. Efficacy of pallidal stimulation in isolated dystonia: a systematic review and meta-analysis. Eur J Neurol. 2017;24(4):552-60.

165. Valldeoriola F, et al. Efficacy and safety of pallidal stimulation in primary dystonia: results of the Spanish multicentric study. J Neurol Neurosurg Psychiatry. 2010;81(1):65-9.

166. Aragao VT, et al. Rescue Subthalamic Deep Brain Stimulation for Refractory Meige Syndrome. Stereotact Funct Neurosurg. 2021;99(5):451-3.

167. Saleh C. How effective is GPi-DBS in the treatment of Meige's syndrome? Parkinsonism Relat Disord. 2011;17(7):569.

168. Reese R, et al. Long-term clinical outcome in meige syndrome treated with internal pallidum deep brain stimulation. Mov Disord. 2011;26(4):691-8.

169. Liu J, et al. Pallidal versus subthalamic deep-brain stimulation for meige syndrome: a retrospective study. Sci Rep. 2021;11(1):8742.

170. Koy A, Timmermann L. Deep brain stimulation in cerebral palsy: Challenges and opportunities. Eur J Paediatr Neurol. 2017;21(1):118-21.

171. Mehdorn HM. Deep brain stimulation for dystonia: review of the literature. J Neurosurg Sci. 2016;60(2):199-210.

172. Loudovici-Krug D, et al. Physiotherapy for Cervical Dystonia: A Systematic Review of Randomised Controlled Trials. Toxins (Basel). 2022;14(11).

173. Queiroz MAR, et al. Physical therapy program for cervical dystonia: a study of 20 cases. Funct Neurol. 2012;27(3):187-92.

174. De Pauw J, et al. The effectiveness of physiotherapy for cervical dystonia: a systematic literature review. J Neurol. 2014;261(10):1857-65.

175. Costanzo M, et al. Effect of Botulinum Toxin on Non-Motor Symptoms in Cervical Dystonia. Toxins (Basel). 2021;13(9).

176. Gimeno H, et al. Beyond the Burke-Fahn-Marsden Dystonia Rating Scale: deep brain stimulation in childhood secondary dystonia. Eur J Paediatr Neurol. 2012;16(5):501-8.

177. Marciniec M, et al. Targeting pain in the long-term treatment of cervical dystonia with botulinum toxin A. Int J Neurosci. 2022;132(10):1026-30.

178. Perides S, et al. Deep brain stimulation reduces pain in children with dystonia, including in dyskinetic cerebral palsy. Dev Med Child Neurol. 2020;62(8):917-25.

179. Kulisevsky J, et al. Bilateral pallidal stimulation for cervical dystonia: dissociated pain and motor improvement. Neurology. 2000;55(11):1754-5.

180. Chudler EH, Dong WK. The role of the basal ganglia in nociception and pain. Pain. 1995;60(1):3-38.

181. Tsuboi T, et al. Quality of life outcomes after deep brain stimulation in dystonia: A systematic review. Parkinsonism Relat Disord. 2020;70:82-93.

182. Jahanshahi M, et al. Neuropsychological, neuropsychiatric, and quality of life issues in DBS for dystonia. Mov Disord. 2011;26 Suppl 1:S63-78.

183. Blahak C, et al. Health-related quality of life in segmental dystonia is improved by bilateral pallidal stimulation. J Neurol. 2008;255(2):178-82.

184. Reese R, Volkmann J. Deep Brain Stimulation for the Dystonias: Evidence, Knowledge Gaps, and Practical Considerations. Movement Disorders Clinical Practice. 2017;4(4):486-94.

185. Schjerling L, et al. A randomized double-blind crossover trial comparing subthalamic and pallidal deep brain stimulation for dystonia. J Neurosurg. 2013;119(6):1537-45.

186. Oliveira DC. The Development and Validation of the Dementia Quality of Life Scale for Older Family Carers (DQOL-OC): University of Nottingham; 2017.

187. Jhangiani R, et al. Reliability and Validity of Measurement. Research Methods in Psychology. 4th ed: Kwantlen Polytechnic University; 2019.

188. Cronbach LJ, Meehl PE. Construct validity in psychological tests. Psychol Bull. 1955;52(4):281-302.

189. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med. 2016;15(2):155-63.

190. Cicchetti DV. Guidelines, Criteria, and Rules of Thumb for Evaluating Normed and Standardized Assessment Instruments in Psychology. Psychological Assessment. 1994;6:284-90.

191. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.

192. Listik C, et al. Development and Validation of the Dystonia-Pain Classification System: A Multicenter Study. Mov Disord. 2023.

193. Harris PA, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.

194. Burke RE, et al. Validity and reliability of a rating scale for the primary torsion dystonias. Neurology. 1985;35(1):73-7.

195. Pais-Ribeiro J, et al. Validation study of a Portuguese version of the Hospital Anxiety and Depression Scale. Psychol Health Med. 2007;12(2):225-35; quiz 35-37.

196. Santos M, Monteiro AL, Santos B. EQ-5D Brazilian population norms. Health Qual Life Outcomes. 2021;19(1):162.

197. Lopes LCG, et al. Beyond weakness: Characterization of pain, sensory profile and conditioned pain modulation in patients with motor neuron disease: A controlled study. European Journal of Pain (London, England). 2018;22(1):72-83.

198. Ferreira KA, et al. Validation of brief pain inventory to Brazilian patients with pain. Support Care Cancer. 2011;19(4):505-11.

199. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain. 1983;17(2):197-210.

200. Santos JG, et al. Translation to Portuguese and validation of the Douleur Neuropathique 4 questionnaire. J Pain. 2010;11(5):484-90.

201. Bouhassira D, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005;114(1-2):29-36.

202. Furr RM. Scale construction and psychometrics for social and personality psychology. 1st ed. London: SAGE; 2011.

203. Lehmann DR, Hulbert J. Are Three-Point Scales Always Good Enough? Journal of Marketing Research. 1972;9(4):444-6.

204. Memon MA, et al. Sample Size for Survey Research: Review and Recommendations. Journal of Applied Structural Equation Modeling. 2020;4(2):i-xx.

205. Park MS, et al. Evaluating test-retest reliability in patient-reported outcome measures for older people: A systematic review. Int J Nurs Stud. 2018;79:58-69.

206. Nelson EC, et al. Patient reported outcome measures in practice. BMJ. 2015;350:g7818.

207. Freynhagen R, et al. Current understanding of the mixed pain concept: a brief narrative review. Curr Med Res Opin. 2019;35(6):1011-8.

208. Erro R, et al. High frequency somatosensory stimulation in dystonia: Evidence fordefective inhibitory plasticity. Mov Disord. 2018;33(12):1902-9.

209. Antelmi E, et al. Neurophysiological correlates of abnormal somatosensory temporal discrimination in dystonia. Mov Disord. 2017;32(1):141-8.

210. Erro R, et al. Reversal of Temporal Discrimination in Cervical Dystonia after Low-Frequency Sensory Stimulation. Mov Disord. 2021;36(3):761-6.

211. Conte A, et al. Abnormal sensory gating in patients with different types of focal dystonias. Mov Disord. 2018;33(12):1910-7.

212. Sa KN, et al. Prevalence of chronic pain in developing countries: systematic review and meta-analysis. Pain Rep. 2019;4(6):e779.

213. Organization. WH. ICD-11 revision. 2023 [Available from: https://icd.who.int/browse11/l-m/en#/http://id.who.int/icd/entity/2019368323.

214. Moisset X, et al. Migraine headaches and pain with neuropathic characteristics: comorbid conditions in patients with multiple sclerosis. Pain. 2013;154(12):2691-9.

215. Treede RD, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain. 2019;160(1):19-27.

216. Organization WH. International Classification of Diseases Eleventh Revision (ICD-11). Geneva2022 [Available from: https://icd.who.int/en.

217. Nicholas M, et al. The IASP classification of chronic pain for ICD-11: chronic primary pain. Pain. 2019;160(1):28-37.

218. Nugraha B, et al. The IASP classification of chronic pain for ICD-11: functioning properties of chronic pain. Pain. 2019;160(1):88-94.

219. Mylius V, et al. Pain sensitivity and clinical progression in Parkinson's disease. Mov Disord. 2011;26(12):2220-5.

220. Grichnik KP, Ferrante FM. The difference between acute and chronic pain. Mt Sinai J Med. 1991;58(3):217-20.

221. Merskey H, Bogduk N. Classification of Chronic Pain. 2nd ed. Seattle: IASP Press; 1994.

222. Johnson Q, Borsheski RR, Reeves-Viets JL. Pain management mini-series. Part I. A review of management of acute pain. Mo Med. 2013;110(1):74-9.

223. Bonica JJ. The management of pain. Philadelphia: Lea & Febiger; 1953.

224. Treede R-D, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain. 2019;160(1):19-27.

225. Treede R-D, et al. A classification of chronic pain for ICD-11. Pain. 2015;156(6):1003-7.

226. Services USDoHaH, et al. Guidance for Industry - Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims 2009. p. 1-39.

APPENDIX

APPENDIX A — Copyright Clearance from John Wiley and Sons and Movement Disorders

JOHN WILEY AND SONS LICENSE
TERMS AND CONDITIONS

May 25, 2023

This Agreement between Dr. Clarice Listik ("You") and John Wiley and Sons ("John Wiley and Sons") consists of your license details and the terms and conditions provided by John Wiley and Sons and Copyright Clearance Center.

License Number	5555860772536
License date	May 25, 2023
Licensed Content Publisher	John Wiley and Sons
Licensed Content Publication	Movement Disorders
Licensed Content Title	Development and Validation of the Dystonia-Pain Classification System: A Multicenter Study
Licensed Content Author	Daniel Ciampi de Andrade, Rubens Gisbert Cury, Sarah Teixeira Camargos, et al
Licensed Content Date	May 20, 2023
Licensed Content Volume	0
Licensed Content Issue	0
Licensed Content Pages	13
Type of use	Dissertation/Thesis
Requestor type	Author of this Wiley article
Format	Print and electronic

Portion	Full article
Will you be translating?	No
Title	CLASSIFYING CHRONIC PAIN IN DYSTONIA: A MULTICENTER STUDY
Institution name	Universidade de Sao Paulo (University of Sao Paulo
Expected presentation date	Jul 2023
Order reference number	1
Requestor Location	Dr. Clarice Listik Rua Afonso Celso 1629 cj 42 Sao PAulo, 04119062 Brazil Attn: Dr. Clarice Listik
Publisher Tax ID	EU826007151
Total	0.00 USD
Terms and Conditions	

TERMS AND CONDITIONS

This copyrighted material is owned by or exclusively licensed to John Wiley & Sons, Inc. or one of its group companies (each a"Wiley Company") or handled on behalf of a society with which a Wiley Company has exclusive publishing rights in relation to a particular work (collectively "WILEY"). By clicking "accept" in connection with completing this licensing transaction, you agree that the following terms and conditions apply to this transaction (along with the billing and payment terms and conditions established by the Copyright Clearance Center Inc., ("CCC's Billing and Payment terms and conditions"), at the time that you opened your RightsLink account (these are available at any time at http://myaccount.copyright.com).

Terms and Conditions

- The materials you have requested permission to reproduce or reuse (the "Wiley Materials") are protected by copyright.

- You are hereby granted a personal, non-exclusive, non-sub licensable (on a stand-alone basis), non-transferable, worldwide, limited license to reproduce the Wiley Materials for the purpose specified in the licensing process. This license, **and any CONTENT (PDF or image file) purchased as part of your order,** is for a one-time use only and limited to any maximum distribution number specified in the license. The first instance of republication or reuse granted by this license must be completed within two years of the date of the grant of this license (although copies prepared before the end date may be distributed thereafter). The Wiley Materials shall not be used in any other manner or for any other purpose, beyond what is granted in the license. Permission is granted subject to an appropriate acknowledgement given to the author, title of the material/book/journal and the publisher. You shall also duplicate the copyright notice that appears in the Wiley publication in your use of the Wiley Material. Permission is also granted on the understanding that nowhere in the text is a previously published source acknowledged for all or part of this Wiley Material. Any third party content is expressly excluded from this permission.

- With respect to the Wiley Materials, all rights are reserved. Except as expressly granted by the terms of the license, no part of the Wiley Materials may be copied, modified, adapted (except for minor reformatting required by the new Publication), translated, reproduced, transferred or distributed, in any form or by any means, and no derivative works may be made based on the Wiley Materials without the prior permission of the respective copyright owner.**For STM Signatory Publishers clearing permission under the terms of the STM Permissions Guidelines only, the terms of the license are extended to include subsequent editions and for editions in other languages, provided such editions are for the work as a whole in situ and does not involve the separate exploitation of the permitted figures or extracts,** You may not alter, remove or suppress in any manner any copyright, trademark or other notices displayed by the Wiley Materials. You may not license, rent, sell, loan, lease, pledge, offer as security, transfer or assign the Wiley Materials on a stand-alone basis, or any of the rights granted to you hereunder to any other person.

- The Wiley Materials and all of the intellectual property rights therein shall at all times remain the exclusive property of John Wiley & Sons Inc, the Wiley Companies, or their respective licensors, and your interest therein is only that of having possession of and the right to reproduce the Wiley Materials pursuant to Section 2 herein during the continuance of this Agreement. You agree that you own no right, title or interest in or to the Wiley Materials or any of the intellectual property rights therein. You shall have no rights hereunder other than the license as provided for above in Section 2. No right, license or interest to any trademark, trade name, service mark or other branding ("Marks") of WILEY or its licensors is granted hereunder, and you agree that you shall not assert any such right, license or interest with respect thereto

- NEITHER WILEY NOR ITS LICENSORS MAKES ANY WARRANTY OR REPRESENTATION OF ANY KIND TO YOU OR ANY THIRD PARTY, EXPRESS, IMPLIED OR STATUTORY, WITH RESPECT TO THE MATERIALS OR THE ACCURACY OF ANY INFORMATION CONTAINED IN THE MATERIALS, INCLUDING, WITHOUT LIMITATION, ANY IMPLIED WARRANTY OF MERCHANTABILITY, ACCURACY, SATISFACTORY QUALITY, FITNESS FOR A PARTICULAR PURPOSE, USABILITY, INTEGRATION OR NON-INFRINGEMENT AND ALL SUCH WARRANTIES ARE HEREBY EXCLUDED BY WILEY AND ITS LICENSORS AND WAIVED BY YOU.

- WILEY shall have the right to terminate this Agreement immediately upon breach of this Agreement by you.

- You shall indemnify, defend and hold harmless WILEY, its Licensors and their respective directors, officers, agents and employees, from and against any actual or threatened claims, demands, causes of action or proceedings arising from any breach

of this Agreement by you.

- IN NO EVENT SHALL WILEY OR ITS LICENSORS BE LIABLE TO YOU OR ANY OTHER PARTY OR ANY OTHER PERSON OR ENTITY FOR ANY SPECIAL, CONSEQUENTIAL, INCIDENTAL, INDIRECT, EXEMPLARY OR PUNITIVE DAMAGES, HOWEVER CAUSED, ARISING OUT OF OR IN CONNECTION WITH THE DOWNLOADING, PROVISIONING, VIEWING OR USE OF THE MATERIALS REGARDLESS OF THE FORM OF ACTION, WHETHER FOR BREACH OF CONTRACT, BREACH OF WARRANTY, TORT, NEGLIGENCE, INFRINGEMENT OR OTHERWISE (INCLUDING, WITHOUT LIMITATION, DAMAGES BASED ON LOSS OF PROFITS, DATA, FILES, USE, BUSINESS OPPORTUNITY OR CLAIMS OF THIRD PARTIES), AND WHETHER OR NOT THE PARTY HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES. THIS LIMITATION SHALL APPLY NOTWITHSTANDING ANY FAILURE OF ESSENTIAL PURPOSE OF ANY LIMITED REMEDY PROVIDED HEREIN.

- Should any provision of this Agreement be held by a court of competent jurisdiction to be illegal, invalid, or unenforceable, that provision shall be deemed amended to achieve as nearly as possible the same economic effect as the original provision, and the legality, validity and enforceability of the remaining provisions of this Agreement shall not be affected or impaired thereby.

- The failure of either party to enforce any term or condition of this Agreement shall not constitute a waiver of either party's right to enforce each and every term and condition of this Agreement. No breach under this agreement shall be deemed waived or excused by either party unless such waiver or consent is in writing signed by the party granting such waiver or consent. The waiver by or consent of a party to a breach of any provision of this Agreement shall not operate or be construed as a waiver of or consent to any other or subsequent breach by such other party.

- This Agreement may not be assigned (including by operation of law or otherwise) by you without WILEY's prior written consent.

- Any fee required for this permission shall be non-refundable after thirty (30) days from receipt by the CCC.

- These terms and conditions together with CCC's Billing and Payment terms and conditions (which are incorporated herein) form the entire agreement between you and WILEY concerning this licensing transaction and (in the absence of fraud) supersedes all prior agreements and representations of the parties, oral or written. This Agreement may not be amended except in writing signed by both parties. This Agreement shall be binding upon and inure to the benefit of the parties' successors, legal representatives, and authorized assigns.

- In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment terms and conditions, these terms and conditions shall prevail.

- WILEY expressly reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment terms and conditions.

- This Agreement will be void if the Type of Use, Format, Circulation, or Requestor Type was misrepresented during the licensing process.

- This Agreement shall be governed by and construed in accordance with the laws of the State of New York, USA, without regards to such state's conflict of law rules. Any legal action, suit or proceeding arising out of or relating to these Terms and Conditions or the breach thereof shall be instituted in a court of competent jurisdiction in New York County in the State of New York in the United States of America and each party hereby consents and submits to the personal jurisdiction of such court, waives any objection to venue in such court and consents to service of process by registered or certified mail, return receipt requested, at the last known address of such party.

WILEY OPEN ACCESS TERMS AND CONDITIONS

Wiley Publishes Open Access Articles in fully Open Access Journals and in Subscription journals offering Online Open. Although most of the fully Open Access journals publish open access articles under the terms of the Creative Commons Attribution (CC BY) License only, the subscription journals and a few of the Open Access Journals offer a choice of Creative Commons Licenses. The license type is clearly identified on the article.

The Creative Commons Attribution License

The Creative Commons Attribution License (CC-BY) allows users to copy, distribute and transmit an article, adapt the article and make commercial use of the article. The CC-BY license permits commercial and non-

Creative Commons Attribution Non-Commercial License

The Creative Commons Attribution Non-Commercial (CC-BY-NC)License permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.(see below)

Creative Commons Attribution-Non-Commercial-NoDerivs License

The Creative Commons Attribution Non-Commercial-NoDerivs License (CC-BY-NC-ND) permits use, distribution and reproduction in any medium, provided the original work is properly cited, is not used for commercial purposes and no modifications or adaptations are made. (see below)

Use by commercial "for-profit" organizations

Use of Wiley Open Access articles for commercial, promotional, or marketing purposes requires further explicit permission from Wiley and will be subject to a fee.

Further details can be found on Wiley Online Library
http://olabout.wiley.com/WileyCDA/Section/id-410895.html

Other Terms and Conditions:

v1.10 Last updated September 2015

Questions? customercare@copyright.com.

APPENDIX B — Copyright Clearance from John Wiley and Sons and Movement Disorders

JOHN WILEY AND SONS LICENSE
TERMS AND CONDITIONS

May 25, 2023

This Agreement between Dr. Clarice Listik ("You") and John Wiley and Sons ("John Wiley and Sons") consists of your license details and the terms and conditions provided by John Wiley and Sons and Copyright Clearance Center.

License Number	5555870015415
License date	May 25, 2023
Licensed Content Publisher	John Wiley and Sons
Licensed Content Publication	Movement Disorders
Licensed Content Title	Development and Validation of the Dystonia-Pain Classification System: A Multicenter Study
Licensed Content Author	Daniel Ciampi de Andrade, Rubens Gisbert Cury, Sarah Teixeira Camargos, et al
Licensed Content Date	May 20, 2023
Licensed Content Volume	0
Licensed Content Issue	0
Licensed Content Pages	13
Type of use	Dissertation/Thesis
Requestor type	Author of this Wiley article
Format	Print and electronic

Portion	Full article
Will you be translating?	Yes, including English rights
Number of languages	1
Title	CLASSIFYING CHRONIC PAIN IN DYSTONIA: A MULTICENTER STUDY
Institution name	Universidade de Sao Paulo (University of Sao Paulo
Expected presentation date	Jul 2023
Order reference number	2
Specific Languages	portuguese
Requestor Location	Dr. Clarice Listik Rua Afonso Celso 1629 cj 42 Sao PAulo, 04119062 Brazil Attn: Dr. Clarice Listik
Publisher Tax ID	EU826007151
Total	0.00 USD
Terms and Conditions	

TERMS AND CONDITIONS

This copyrighted material is owned by or exclusively licensed to John Wiley & Sons, Inc. or one of its group companies (each a"Wiley Company") or handled on behalf of a society with which a Wiley Company has exclusive publishing rights in relation to a particular work (collectively "WILEY"). By clicking "accept" in connection with completing this licensing transaction, you agree that the following terms and conditions apply to this transaction (along with the billing and payment terms and conditions established by the Copyright Clearance Center Inc., ("CCC's Billing and Payment terms and conditions"), at the time that you opened your RightsLink account (these are available at any time at http://myaccount.copyright.com).

Terms and Conditions

- The materials you have requested permission to reproduce or reuse (the "Wiley Materials") are protected by copyright.

- You are hereby granted a personal, non-exclusive, non-sub licensable (on a stand-alone basis), non-transferable, worldwide, limited license to reproduce the Wiley Materials for the purpose specified in the licensing process. This license, **and any CONTENT (PDF or image file) purchased as part of your order,** is for a one-time use only and limited to any maximum distribution number specified in the license. The first instance of republication or reuse granted by this license must be completed within two years of the date of the grant of this license (although copies prepared before the end date may be distributed thereafter). The Wiley Materials shall not be used in any other manner or for any other purpose, beyond what is granted in the license. Permission is granted subject to an appropriate acknowledgement given to the author, title of the material/book/journal and the publisher. You shall also duplicate the copyright notice that appears in the Wiley publication in your use of the Wiley Material. Permission is also granted on the understanding that nowhere in the text is a previously published source acknowledged for all or part of this Wiley Material. Any third party content is expressly excluded from this permission.

- With respect to the Wiley Materials, all rights are reserved. Except as expressly granted by the terms of the license, no part of the Wiley Materials may be copied, modified, adapted (except for minor reformatting required by the new Publication), translated, reproduced, transferred or distributed, in any form or by any means, and no derivative works may be made based on the Wiley Materials without the prior permission of the respective copyright owner.**For STM Signatory Publishers clearing permission under the terms of the STM Permissions Guidelines only, the terms of the license are extended to include subsequent editions and for editions in other languages, provided such editions are for the work as a whole in situ and does not involve the separate exploitation of the permitted figures or extracts,** You may not alter, remove or suppress in any manner any copyright, trademark or other notices displayed by the Wiley Materials. You may not license, rent, sell, loan, lease, pledge, offer as security, transfer or assign the Wiley Materials on a stand-alone basis, or any of the rights granted to you hereunder to any other person.

- The Wiley Materials and all of the intellectual property rights therein shall at all times remain the exclusive property of John Wiley & Sons Inc, the Wiley Companies, or their respective licensors, and your interest therein is only that of having possession of and the right to reproduce the Wiley Materials pursuant to Section 2 herein during the continuance of this Agreement. You agree that you own no right, title or interest in or to the Wiley Materials or any of the intellectual property rights therein. You shall have no rights hereunder other than the license as provided for above in Section 2. No right, license or interest to any trademark, trade name, service mark or other branding ("Marks") of WILEY or its licensors is granted hereunder, and you agree that you shall not assert any such right, license or interest with respect thereto

- NEITHER WILEY NOR ITS LICENSORS MAKES ANY WARRANTY OR REPRESENTATION OF ANY KIND TO YOU OR ANY THIRD PARTY, EXPRESS, IMPLIED OR STATUTORY, WITH RESPECT TO THE MATERIALS OR THE ACCURACY OF ANY INFORMATION CONTAINED IN THE MATERIALS, INCLUDING, WITHOUT LIMITATION, ANY IMPLIED WARRANTY OF MERCHANTABILITY, ACCURACY, SATISFACTORY QUALITY, FITNESS FOR A PARTICULAR PURPOSE, USABILITY, INTEGRATION OR NON-INFRINGEMENT AND ALL SUCH WARRANTIES ARE HEREBY EXCLUDED BY WILEY AND ITS LICENSORS AND WAIVED BY YOU.

- WILEY shall have the right to terminate this Agreement immediately upon breach of this Agreement by you.

- You shall indemnify, defend and hold harmless WILEY, its Licensors and their respective directors, officers, agents and employees, from and against any actual or threatened claims, demands, causes of action or proceedings arising from any breach of this Agreement by you.

- IN NO EVENT SHALL WILEY OR ITS LICENSORS BE LIABLE TO YOU OR ANY OTHER PARTY OR ANY OTHER PERSON OR ENTITY FOR ANY SPECIAL, CONSEQUENTIAL, INCIDENTAL, INDIRECT, EXEMPLARY OR PUNITIVE DAMAGES, HOWEVER CAUSED, ARISING OUT OF OR IN CONNECTION WITH THE DOWNLOADING, PROVISIONING, VIEWING OR USE OF THE MATERIALS REGARDLESS OF THE FORM OF ACTION, WHETHER FOR BREACH OF CONTRACT, BREACH OF WARRANTY, TORT, NEGLIGENCE, INFRINGEMENT OR OTHERWISE (INCLUDING, WITHOUT LIMITATION, DAMAGES BASED ON LOSS OF PROFITS, DATA, FILES, USE, BUSINESS OPPORTUNITY OR CLAIMS OF THIRD PARTIES), AND WHETHER OR NOT THE PARTY HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES. THIS LIMITATION SHALL APPLY NOTWITHSTANDING ANY FAILURE OF ESSENTIAL PURPOSE OF ANY LIMITED REMEDY PROVIDED HEREIN.

- Should any provision of this Agreement be held by a court of competent jurisdiction to be illegal, invalid, or unenforceable, that provision shall be deemed amended to achieve as nearly as possible the same economic effect as the original provision, and the legality, validity and enforceability of the remaining provisions of this Agreement shall not be affected or impaired thereby.

- The failure of either party to enforce any term or condition of this Agreement shall not constitute a waiver of either party's right to enforce each and every term and condition of this Agreement. No breach under this agreement shall be deemed waived or excused by either party unless such waiver or consent is in writing signed by the party granting such waiver or consent. The waiver by or consent of a party to a breach of any provision of this Agreement shall not operate or be construed as a waiver of or consent to any other or subsequent breach by such other party.

- This Agreement may not be assigned (including by operation of law or otherwise) by you without WILEY's prior written consent.

- Any fee required for this permission shall be non-refundable after thirty (30) days from receipt by the CCC.

- These terms and conditions together with CCC's Billing and Payment terms and conditions (which are incorporated herein) form the entire agreement between you and WILEY concerning this licensing transaction and (in the absence of fraud) supersedes all prior agreements and representations of the parties, oral or written. This Agreement may not be amended except in writing signed by both parties. This Agreement shall be binding upon and inure to the benefit of the parties' successors, legal representatives, and authorized assigns.

- In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment terms and conditions, these terms and conditions shall prevail.

- WILEY expressly reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment terms

and conditions.

- This Agreement will be void if the Type of Use, Format, Circulation, or Requestor Type was misrepresented during the licensing process.

- This Agreement shall be governed by and construed in accordance with the laws of the State of New York, USA, without regards to such state's conflict of law rules. Any legal action, suit or proceeding arising out of or relating to these Terms and Conditions or the breach thereof shall be instituted in a court of competent jurisdiction in New York County in the State of New York in the United States of America and each party hereby consents and submits to the personal jurisdiction of such court, waives any objection to venue in such court and consents to service of process by registered or certified mail, return receipt requested, at the last known address of such party.

WILEY OPEN ACCESS TERMS AND CONDITIONS

Wiley Publishes Open Access Articles in fully Open Access Journals and in Subscription journals offering Online Open. Although most of the fully Open Access journals publish open access articles under the terms of the Creative Commons Attribution (CC BY) License only, the subscription journals and a few of the Open Access Journals offer a choice of Creative Commons Licenses. The license type is clearly identified on the article.

The Creative Commons Attribution License

The Creative Commons Attribution License (CC-BY) allows users to copy, distribute and transmit an article, adapt the article and make commercial use of the article. The CC-BY license permits commercial and non-

Creative Commons Attribution Non-Commercial License

The Creative Commons Attribution Non-Commercial (CC-BY-NC)License permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.(see below)

Creative Commons Attribution-Non-Commercial-NoDerivs License

The Creative Commons Attribution Non-Commercial-NoDerivs License (CC-BY-NC-ND) permits use, distribution and reproduction in any medium, provided the original work is properly cited, is not used for commercial purposes and no modifications or adaptations are made. (see below)

Use by commercial "for-profit" organizations

Use of Wiley Open Access articles for commercial, promotional, or marketing purposes requires further explicit permission from Wiley and will be subject to a fee.

Further details can be found on Wiley Online Library
http://olabout.wiley.com/WileyCDA/Section/id-410895.html

Other Terms and Conditions:

v1.10 Last updated September 2015

APPENDIX C — Ethics Commission’s approval of the project.

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Classificação de dor e sintomas não-motores em pacientes distônicos.
Pesquisador: Daniel Ciampia Araujo de Andrade
Área Temática:
Versão: 1
CAAE: 31832920.2.0000.0068
Instituição Proponente: Hospital das Clínicas da Faculdade de Medicina da USP
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.093.866

Apresentação do Projeto:
Trata-se da apresentação do projeto "Classificação de dor e sintomas não-motores em pacientes distônicos". É um estudo transversal, com o objetivo de avaliar de dor e outros sintomas não-motores nas distonias. A amostra é de conveniência, com 140 pacientes. A escala a ser aplicada é a escala de avaliação da distonia de Burke-Marsden-Fahn.

Objetivo da Pesquisa:
O objetivo da pesquisa é avaliar de dor e outros sintomas não-motores nas distonias. Primariamente, o estudo pretende classificar a dor de pacientes distônicos.
Secundariamente, pretende-se realizar uma classificação e escala de dor em pacientes distônicos e avaliar sintomas não-motores (psiquiátricos, cognitivos, sono, autonômicos) na distonia.

Avaliação dos Riscos e Benefícios:
Os riscos são considerados mínimos, uma vez que apenas questionários serão aplicados.
Os benefícios do estudo são indiretos, pois poderá auxiliar a compreensão da dor que ocorre em pacientes distônicos, a fim de separá-la em tipos diferentes para que estudos futuros possam aprofundar as possíveis intervenções.
melhores formas de melhor a dor na distonia.

Comentários e Considerações sobre a Pesquisa:
Nada a comentar.

Considerações sobre os Termos de apresentação obrigatória:

O TCLE está escrito em formato de carta convite, esclarecendo os procedimentos em linguagem adequada.

Recomendações:

Nada a recomendar.

Conclusões ou Pendências e Lista de Inadequações:

Projeto aprovado, sem pendências ou inadequações.

Considerações Finais a critério do CEP:

Em conformidade com a Resolução CNS nº 466/12 – cabe ao pesquisador: a) desenvolver o projeto conforme delineado; b) elaborar e apresentar relatórios parciais e final; c)apresentar dados solicitados pelo CEP, a qualquer momento; d) manter em arquivo sob sua guarda, por 5 anos da pesquisa, contendo fichas individuais e todos os demais documentos recomendados pelo CEP; e) encaminhar os resultados para publicação, com os devidos créditos aos pesquisadores associados e ao pessoal técnico participante do projeto; f) justificar perante ao CEP interrupção do projeto ou a não publicação dos resultados.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1527513.pdf	13/05/2020 17:03:54		Aceito
Folha de Rosto	CEP.pdf	13/05/2020 17:00:53	Daniel Ciampia Araujo de Andrade	Aceito
Outros	carta_compromisso_doutorado.pdf	07/05/2020 19:29:15	Daniel Ciampia Araujo de Andrade	Aceito
Outros	dados_digitais.pdf	07/05/2020 19:28:48	Daniel Ciampia Araujo de Andrade	Aceito
Outros	aprovacao_departamento.pdf	07/05/2020 19:27:49	Daniel Ciampia Araujo de Andrade	Aceito
Outros	escala_sintomas_nao_motores.pdf	07/05/2020 19:26:24	Daniel Ciampia Araujo de Andrade	Aceito
Outros	Dados_Pessoais.pdf	07/05/2020 19:25:28	Daniel Ciampia Araujo de Andrade	Aceito
Outros	Classificacao.docx	07/05/2020 19:24:19	Daniel Ciampia Araujo de Andrade	Aceito
Outros	BFM.doc	07/05/2020 19:23:18	Daniel Ciampia Araujo de Andrade	Aceito

Outros	EuroQol.pdf	07/05/2020 19:23:03	Daniel Ciampia Araujo de Andrade	Aceito
Outros	Dor.pdf	07/05/2020 19:22:24	Daniel Ciampia Araujo de Andrade	Aceito
Outros	Distonia.pdf	07/05/2020 19:22:13	Daniel Ciampia Araujo de Andrade	Aceito
Outros	FAB.pdf	07/05/2020 19:21:43	Daniel Ciampia Araujo de Andrade	Aceito
Cronograma	Cronograma.docx	07/05/2020 19:18:43	Daniel Ciampia Araujo de Andrade	Aceito
Orçamento	SEM_CUSTO.pdf	07/05/2020 19:18:09	Daniel Ciampia Araujo de Andrade	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_atual.docx	07/05/2020 19:16:53	Daniel Ciampia Araujo de Andrade	Aceito
Projeto Detalhado / Brochura Investigador	Projeto.docx	07/05/2020 19:16:34	Daniel Ciampia Araujo de Andrade	Aceito
Outros	Curriculo_Clarice.pdf	17/03/2020 14:39:50	Daniel Ciampia Araujo de Andrade	Aceito
Outros	Curriculo_Ciampi.pdf	17/03/2020 14:39:32	Daniel Ciampia Araujo de Andrade	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SAO PAULO, 17 de Junho de 2020

Assinado por:
ALFREDO JOSE MANSUR
(Coordenador(a))

APPENDIX D — Ethics Commission’s approval of the project

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação de dor e sintomas não-motores em pacientes distônicos
Pesquisador: Flávia de Paiva Santos Rolim
Área Temática:
Versão: 4
CAAE: 43188521.4.1001.5040
Instituição Proponente: Hospital Geral de Fortaleza/SUS
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.719.855

Apresentação do Projeto:
A distonia é um grupo complexo e heterogêneo de doenças que pode decorrer de causas adquiridas, hereditárias ou idiopáticas. Nas últimas
décadas, houve uma grande busca de conhecimento e pesquisa na área da distonia abrangendo desde a sua genética, base fisiopatológica e
clínica, até seus tratamentos medicamentosos e cirúrgicos. Apesar dos muitos avanços, há um amplo campo de estudo nas distonias ainda a ser
explorado. O foco principal sempre foram as alterações motoras que são de grande importância, além de serem a parte mais visível e direta deste
conjunto de doenças. Há, ainda, uma paucidade de estudos cujo foco principal seja os aspectos não-motores das distonias, menos flagrantes, mas
não menos importantes. Os sintomas não motores, principalmente a dor, afetam muito a qualidade de vida dos pacientes distônicos, com impacto
em sua vida pessoal, social, estudo e trabalho.O presente estudo busca analisar aspectos não-motores da distonia com ênfase em dor, classificar o
tipo de dor presente em pacientes distônicos e caracterizar melhor outros sintomas não-motores (sono, cognitivo, autonômico, psiquiátricos e
sensitivos).1.1 Diagnóstico clínico e classificação das distoniasA distonia é um distúrbio do movimento caracterizado por contrações musculares

sustentadas ou intermitentes causando movimentos e/ou posturas anormais, frequentemente repetitivas. Os movimentos distônicos são tipicamente
padronizados, torcionais e podem ser tremulantes. A distonia é frequentemente iniciada ou agravada por ações voluntárias e associadas com um
overflow de ativações musculares (1). Seu diagnóstico é clínico baseado na fenomenologia dos movimentos apresentados pelo paciente.A
classificação mais moderna de distonia é a publicada em 2013 (1) e separa as síndromes distônicas em dois eixos: características clínicas e
etiologia (vide Tabela 1). Tabela 1 - Classificação das distonias.Eixo I. Características ClínicasCaracterísticas clínicas da distonia Idade de início
1. Infância (nascimento aos 2 anos) 2. Escolar (3 aos 12 anos) 3. Adolescência (13 anos 20 anos) 4. Idade adulta precoce (21
aos 40 anos) 5. Idade adulta tardia (> 40 anos)Distribuição corporal 1. Focal 2. Segmentar 3. Multifocal
4. Generalizada (com e sem acometimento dos membros inferiores) 5. HemidistoniaPadrão temporal Curso da doença 1. Estática
2. ProgressivaVariabilidade 1. Persistente 2. Ação específica 3. Diurna 4. ParoxísticaCaracterísticas associadas
1. Distonia isolada 2. Distonia combinada com outros distúrbios do movimento Presença de outras manifestações neurológicas ou
sistêmicasTabela 1 (continuação)Eixo II. EtiologiaEtiologia Patologia do Sistema Nervoso Central Evidências de neurodegeneração
Evidência de lesão estrutural (frequentemente estática) Sem evidência de Neurodegeneração ou lesão estrutural Causas Hereditárias ou
Adquiridas Hereditárias Autossômica Dominante Autossômica Recessiva Ligada ao X Mitocondrial
Adquiridas Injúria Perinatal Infecção Tóxica Drogas Vascular Neoplásica Injúria Cerebral
Psicogênica Idiopática Esporádica FamilialAs distonias podem ser isoladas, nas formas em que só há distonia ou tremor
distônico, ou combinadas, as previamente denominadas distonias-plus, com outros distúrbios do movimento com lassifica o ou lassific. O termo
distonia primária não é mais utilizado, pois historicamente designava formas que apresentavam apenas distonia ou tremor distônico, sem ter
alteração patológica identificável. O antigo termo distonia secundária também não é atualmente

utilizado, pois poderia designar tanto uma forma de
distonia não-isolada, quanto uma causa patológica identificável.As diferentes etiologias de distonias têm progressões diferentes. A maioria das
formas de distonia inicialmente tendem a uma piora, como alguns tipos de distonias focais que se generalizam. Porém, as distonias não
neurodegenerativas geralmente atigem um platô e não progridem, enquanto as neurodegenerativas têm um curso lentamente progressivo. Além
disso, algumas formas de distonia são responsivas a levodopa (DYT5) ou ao álcool (DYT11). Em relação a etiologia, as distonias podem ter causas
adquiridas, como infecções, sofrimento perinatal, ou neoplasias; hereditárias como heranças autossômicas dominantes, recessivas, ligadas ao X, ou
mitocondriais; e idiopáticas. As formas monogênicas são referidas com a sigla DYT e acrescidas do número com a ordem em que foram
descobertas.1.2 Sintomas não-motores nas distoniasAs características não motoras das distonias não são tão claramente definidas, sendo pouco
estudadas até o momento, apesar do prejuízo na qualidade de vida dos pacientes. Estes incluem alterações psiquiátricas, como ansiedade e
depressão); cognitivas, autonômicas, de sensibilidade, dor e do sono (2).Quanto às alterações psiquiátricas, pacientes com distonia apresentam
maiores taxas de depressão e ansiedade, com prevalência, segundo uma revisão feita por Kuyper e colaboradores (2011), entre 12 – 71%, sendo a
maioria entre 25 – 50%) (2). Ainda não se sabe se essas alterações psiquiátricas são características primárias das distonias ou se as manifestações
seriam secundárias as manifestações motoras. Porém, um estudo de Wenzel e colaboradores avaliando pacientes com torcicolo espasmódico
mostrou que quase metade dos pacientes apresentavam os sintomas psiquiátricos antes do início do lassific do movimento (3). A maioria dos dados
sobre doenças psiquiátricas em pacientes distônicos advém de estudos com distonia cervical (4). Uma análise, em especial, avalia depressão e
ansiedade em pacientes com distonia cervical, verificando que 40% dos pacientes apresentavam transtornos de ansiedade, 37,5% transtorno
depressivo maior, sendo que 42,5% dos pacientes preenchiam critérios antes do início da distonia cervical (5). Apesar desses estudos poderem

conter um viés de recordação, é possível que a fisiopatologia das distonias predisponha os pacientes a transtorno do humor, entre outras
morbidades psiquiátricas.Outro estudo de Lewis e colaboradores com pacientes de múltiplas formas de distonia revelou que 30% dos pacientes
apresentavam depressão moderada a grave (6). Outros transtornos psiquiátricos evidenciados nas distonias são transtornos do pânico, transtorno
obsessivo-compulsivo, e abuso e dependência de substâncias ilícitas ou lícitas (2,3,7).Em relação às alterações cognitivas nas distonias, os
pacientes não parecem ter déficits significativos na habilidade intelectual, atenção, memória, linguagem ou nas funções executivas quando
comparados aos indivíduos saudáveis (4). Porém, os pacientes distônicos podem ter déficits da função visuoespacial, pior fluência verbal semântica,
e maior susceptibilidade a interferência (4). Já pacientes com distonia adquirida como distonia tardia por fármacos para esquizofrenia ou pacientes
com neurodegeneração associada a pantotenato quinase (PKAN), originalmente conhecida como Síndrome de Hallervorden-Spatz, frequentemente
apresentam déficits cognitivos associados. Evidências mais concretas são difíceis de serem comprovadas por questões metodológicas tais como
amostras pequenas e heterogêneas, e ausência de grupos controle (4).Já quanto a disfunções autonômicas, pouquíssimos estudos avaliaram seus
sintomas. Alguns sintomas como obstipação, retenção urinária, xerostomia podem ser causados por tratamento com anticolinérgicos e com toxina
botulínica. Alguns pacientes com distonia cervical submetidos a toxina botulínica do tipo A têm anormalidades subclínicas na regulação autonômica
cardiovascular e na sensibilidade do barorreflexo cardiopulmonar (8).A distonia impacta importantemente qualidade de vida de seus portadores,
principalmente em relação as funções físicas, sociais e atividades de lazer (9). A distonia também traz dificuldade quanto a empregabilidade, vida
familiar e renda (10,11).1.2.1. A sensibilidade e dor nas DistoniasA dor na distonia é incapacitante e traz prejuízo à qualidade de vida dos pacientes (11,12). Não existem critérios específicos para a
classificação da dor nas distonias (13), refletindo também a escassez de estudos focados em dor nas distonias (7). A maioria dos pacientes
distônicos relata dor musculoesquelética e/ou miofacial.Muitos autores descrevem para a distonia

cervical dor local com irradiação e com a sensação
de um “repuxão” (14). Entretanto, várias evidências demonstram que a dor nas distonias não tem origem apenas muscular (13). Além disso, a
gravidade da distonia pode não corresponder a intensidade ou presença da dor (14,15). Apesar de muitos pacientes relatarem dor, o exame clínico
sensitivo habitual e os testes neurofisiológicos são, em geral, normais (16). Porém, alguns estudos demonstram alterações da grafestesia em
pacientes com distonia focal (17). Pacientes distônicos também apresentam percepção anormal da ilusão de movimento induzida por vibração (18)
sugerindo uma disfunção central do processamento dos sinais aferentes das fibras Ia (16).Como especificado anteriormente, diversos estudos
demonstram que nas distonias há envolvimento dos sistemas sensitivos, incluindo processamento anormal e alteração da discriminação temporal e
espacial de estímulos táteis (19,20). Além disso, alguns estudos revelam que as terapias para distonia como toxina botulínica (21) e ECP (22) não
corrigem essa discriminação temporal anormal.Uma maneira de investigar a integridade somatossensitiva é através de teste de sensibilidade
quantitativo (TSQ) (23), que se trata de um método que avalia qualidades sensitivas diferentes: frio, calor, dor, pressão e vibração. Um estudo prévio
de Paracka e colaboradores já avaliou pacientes com distonias focais, segmentares e generalizadas sem ECP (23). Ele evidenciou que o TSQ pode
detectar anormalidades sensitivas sutis em pacientes com distonia, mesmo sem déficits sensitivos aparentes. Seus principais achados foram o limiar
de detecção ao frio (LDF) diminuído e o aumento da alodínea mecânica dinâmica. Neste estudo, alterações sensitivas sutis foram detectadas nas
mãos dos pacientes com distonia cervical, demonstrando que mesmo regiões sem a distonia apresentam alterações silenciosas.Outra informação
interessante é que não houve relação entre as alterações no TSQ e a gravidade da distonia. Apenas outro estudo utilizou o TSQ em pacientes com
distonia (24). Ele estudou pacientes com cãimbra do escrivão e evidenciou um aumento do LDF, do limiar de detecção ao quente (LDQ) e do limiar
de detecção de dor mecânico (LdoM) em relação aos voluntários saudáveis quando comparados com o membro superior afetado. O LDF e LDQ

também eram maiores na comparação entre o lado afetado e não afetados dos pacientes distônicos. Uma das explicações para a dor nas distonias
pode ser a redução do limiar de dor (2). Um estudo evidenciou um limiar de dor a pressão duas vezes menor em pacientes distônicos na
comparação com voluntários saudáveis (25). Este mesmo estudo também mostrou o limiar de dor reduzido em músculos não afetados pela distonia,
podendo-se levantar a hipótese de uma alteração no processamento da dor nestes pacientes. Alterações no sistema somatossensitivo nos pacientes
distônicos também podem estar envolvidas no mecanismo da dor, como a representação anormal de partes do corpo; e na excitabilidade em testes
neurofisiológicos (15).Outras morbidades associadas, como alterações do sono e depressão, também têm influência na dor (2,26). Há evidências de
melhora da dor com toxina botulínica e fisioterapia (27).Dessa forma, na literatura, ainda não existe um sistema de classificação de dor nas distonias
(28). Ela é provavelmente multifatorial com componentes relacionados as contrações musculares que causam movimentos, espasmos e posturas
anormais (29), mas também relacionada a uma alteração do processamento de dor (23–25) e das vias modulatórias descendentes de dor (30), pois
nem sempre o efeito no componente doloroso está relacionado com a resposta motora dos tratamentos (14,31) ou intensidade dos sintomas
motores (14,29).1.3 FisiopatologiaA fisiopatologia das distonias ainda não é muito conhecida. Algumas alterações neurofisiológicas vêm sendo
identificadas como: redução da inibição cortical, alteração da plasticidade sináptica e a disfunção do processamento sensitivo (32,33).Devido a
grande heterogenicidade quanto a etiologia das distonias é provável que diferentes formas de distonias apresentem origens neuroanatomicas
diferentes, apesar de terem um possível substrato comum (34). A alteração de mecanismos de inibição em vários níveis do sistema nervoso central
pode explicar algumas características clínicas das distonias como o overflow (35), também chamado de transbordamento que é uma contração
muscular não-intencional, geralmente no pico do movimento distônico que se estende além da região do corpo envolvida pela distonia, e a cocontração
de músculos antagonistas (36). No final do século passado, atráves do auxílio da neurofisiologia

identificou-se a perda de inibição em
pacientes com distonia de membro superior (37,38) e anormalidades no reflexo do piscamento (39) em pacientes com blefaroespasmo. A conclusão
da análise desses estudos foi a de que a disfunção da inibição poderia estar relacionada a disfunção do circuito córtico-estriado-tálamo-cortical (32).
Isso explicaria a dificuldade em selecionar o movimento adequado e em inibir o movimento indesejado (32).A nível cortical, estudos com estimulação
magnética transcraniana, demonstraram redução da inibição atráves de perda da inibição intracortical curta e longa, além de um encurtamento do
período silente (do inglês, lassif period) (32). Há também evidências de perda da surround inibition (32,35,36). Esta é um mecanismo fisiológico para
focar a atividade neuronal e selecionar as respostas neuronais (40). Ela é bem conhecida nos sistemas sensitivos, nos quais os sinais mais centrais
são facilitados, e os mais excêntricos, inibidos, aumentando o contraste entre eles (40). No sistema motor, a surround inibition ajuda a selecionar a
execução dos movimentos desejados através da transmissão GABAérgica (40). Além disso, também ocorre um espraiamento anormal de facilitação
nas distonias (32,36). A plasticidade neuronal aumentada ou aberrante leva a conexões disfuncionais. Ela foi demonstrada nas distonias utilizando a
técnica PAS (do inglês, Paired Associative Stimulation) de Estimulação Magnética Transcraniana (EMT) (35). É um paradigma que consiste na
lassifica repetitiva lenta de baixa frequência do nervo mediano combinada com a lassifica magnética transcranina do córtex motor contralateral
(41). Esta técnica revelou um plasticidade anormal semelhante a potenciação de longa duração (PLD ou em inglês long term potentiation) (42). A
PLD é um tipo de plasticidade sináptica, a capacidade das sinapses químicas de mudar sua potência ou força. Um estudo com paciente com
distonia cervical mostrou que quanto maior a neuroplasticidade, mais grave era o acometimento funcional e melhor sua resposta com a ECP, sendo
que a avaliação pela PAS pode ser um preditor do resultado pós-operatório (43).Além disso, um modelo para as distonias tarefa específicas focais
de mão, como a cãimbra do escrivão e algumas distonias em músicos, é o da hipótese dos dois fatores: o primeiro fator seria ambiental, como

disfunção periférica ou treinamento repetitivo e o segundo fator seria a existência de alterações sutis nos mecanismos de plasticidade nos circuitos
sensitivo-motores (35). Porém, os fatores ambientais só levariam à distonia se estiverem sobrepostos a uma alteração latente da plasticidade
(35).Existem diversas evidências que apontam para uma contribuição de anormalidades sensitivas na fisiopatologia das distonias. Sintomas
sensitivos são frequentes nas distonias focais e manipulação sensitiva pode modificar os movimentos distônicos, os chamados truques sensitivos
(16). Os truques sensitivos, também conhecidos como geste antagoniste, resultam na melhora parcial ou total das posturas distônicas ou dos
movimentos distônicos. Há vários estudos com eletrofisiologia buscando explicação para os truques sensitivos, acredita-se que eles diminuem o
desbalanço cortical da facilitação/inibição (44).Organizações anormais de mapas somatossensitivos corticais, que podem levar a alteração da
representação cortical de partes do corpo no córtex somatossensitivo; bem como anormalidades na integração sensitivo-motora e no processamento
sensitivo podem estar envolvidas (19). Os métodos de imagem em pacientes com distonia tando adquiridas quanto não, mostram alterações
estruturais como aumento da densidade da substância cinzenta no córtex sensitivo primário e aumento volumétrico nos núcleos da base (42).
Também demonstram alterações funcionais como atividade anormal no córtex sensitivo motor, área motora suplementar e córtex pré-motor durante
tarefas motoras (42). Estudos com PET (do inglês, Positron Emission Tomography) evidenciaram aumento do metabolismo de glicose basal no
núcleo lentiforme e no córtex pré-motor, além de alteração no receptor D2 de dopamina no putâmen. Esta ligação está diminuída nas distonias
focais e na DYT1 e aumentada na distonia dopa-responsiva (42).1.3.1. A Fisiopatologia dos circuitosOs núcleos da base têm um grande papel na
fisiopatologia das distonias, mas achados mais recentes apontam para o envolvimento, também, de outras regiões, em particular do cerebelo (34).
Assim, a distonia pode ser definida como uma doença de circuitos, envolvendo, tanto o circuito núcleos da base-tálamo-cortical, quanto o cerebelotálamo-
cortical (34). O modelo clássico propõem que a distonia ocorre pela disfunção dos núcleos da base

através do desbalanço entre as vias
direta excitatória e indireta (45). O estriado e o núcleo subtalâmico (NST) recebem informações advindas do córtex organizadas topograficamente
(input). Já o globo pálido interno (Gpi) e substância negra pars reticulata (SNr), são a via de saída para o tálamo (output), feita atráves de projeções
inibitórias que inibem a projeção tálamo-cortical. As conexões entre o estriado e as estruturas que compõem a via de saída para o tálamo são
organizadas em predominantemente duas vias principais: a direta apresenta sinapse inibitória feita atráves do ácido gama-aminobutírico (GABA), já a via indireta é organizada em polissinapses que inclui alvos como o NST e o globo
pálido externo (Gpe) e tem um efeito de rede excitatório sobre as estruturas da via de saída para o tálamo.O balanço entre a via direta e a indireta é
regulado pelas diferentes ações da dopamina no estriado atráves de neurônios da substâncnia negra pars compacta (SNc). A dopamina agindo nos
receptores de dopamina D1 aumenta atividade da via direta, enquanto nos receptores D2 agem sobre a via indireta.Nas distonias, há aumento da
atividade da via indireta e anormalidades da descarga dos neurônios no Gpi. Porém, ao contrário do que ocorre na Doença de Parkinson, nas
distonias a via direta também parece estar com atividade aumentada. Alterações no padrão de atividade, bem como de sincronia das descargas
devem ser mais responsáveis para as manifestações da doença do que o aumento da atividade tálamo-cortical (45).Outra via, a via hiperdireta é
proposta ligando o córtex ao NST (46). Mais recentemente, vem se sedimentando uma outra possível via hiperdireta, a via córtico-palidal, assim o
circuito entre o córtex e os núcleos da base é composto por diversas alças paralelas, segregadas e funcionalmente distintas (47). Figura 1 – Modelo
atual proposto das conexões dos núcleos da base. O input cortical para os núcleos da base ocorre por meio das projeções córtico-estriatais e córtico
-subtalâmicas. As projeções dos núcleos da base que retornam ao córtex (output) originam-se no globo pálido interno e da substância negra pars
reticulata, passando através dos núcleos ventrais talâmicos. A via direta é monossináptica e inibitória, enquanto a via indireta excitatória e uma rede
polissináptica. D1, D2 – Receptores dopaminérgicos.O estriado, caudado e putâmen, pode ser

compreendido em duas partes distintas: a matriz e os
estriossomos que estão dispostas num padrão em mosaico (48). A matriz forma as vias indireta e direta, enquanto a via dos estriossomos exerce
modulação nas vias de saída dopaminérgicas nigrais, exercendo um controle motor adicional. Assim, a regulação dos movimentos pelos núcleos da
base depende da atividade equilibrida destas três vias. Nas distonias, os circuitos envolvendo os núcleos da base tem taxa de despolarização
menor, com padrões alterados entre outras alterações fisiológicas. É postulado que o aumento da atividade estriatal possa ocorrer por perda de
neurônios de projeção estriatal, dos estriosomos ou da matriz, levando a um desbalanço das vias diretas e indiretas (49), porém mais estudos ainda
são necessários.Além disso, há evidências de envolvimento também do circuito cerebelo-tálamo-cortical nas distonias, modificando o conceito de
que a distonia é uma doença apenas dos núcleos da base. Estudos com neuroimagem mostram anormalidades neste circuito, bem como estudos em animais (49).Metodologia Proposta:
Tipo de estudoEste estudo envolve indivíduos com diagnóstico de distonia de qualquer etiologia (adquirida, hereditária ou idiopática) e de qualquer
distribuição (focal, segmentar, multifocal, generalizada, hemidistonia). É um estudo multicêntrico, transversal, para avaliar de dor e outros sintomas
não-motores nas distonias, no qual a maioria dos pacientes será avaliada apenas uma única vez. A outra parte dos pacientes (40) será avaliada até
duas vezes para validação da classificação – intra e inter-examinadores.A avaliação dos pacientes e a coleta de dados serão realizadas no
Ambulatório de Distúrbios do Movimento do Hospital Geral de Fortaleza, nos Ambulatórios de Toxina Botulínica do Hospital Geral de Fortaleza, no
Ambulatório de Neurocirurgia Funcional do Instituto de Psiquiatria do HC-FMUSP, no Ambulatório de Distúrbios do Movimento e em Ambulatórios de
Toxina Botulínica HC-FMUSP, em São Paulo. A avaliação dos pacientes será iniciada em março de 2020 até conseguirmos o número almejado de
pacientes, com término previsto no segundo semestre de 2022. Este projeto é um estudo transversal para avaliação de dor e outros sintomas nãomotores.
Buscamos avaliar 140 pacientes com diversas formas de distonia. Este número é uma amostra de conveniência. Para uma classificação de

onze itens, utilizando a regra de multiplicar por dez cada item (50), precisaríamos 110 pacientes, chegamos a uma amostra de 140, contabilizando o
número de perda de pacientes ao longo do tempo. Quarenta pacientes terão que ser avaliados (apenas aplicando novamente a classificação de dor)
para validação intra e inter-examinadores.
Critério de Inclusão:
1. Paciente com diagnóstico clínico de distonia conforme os critérios internacionais atuais
2. Pacientes maiores de 18 anos
3. Pacientes intelectualmente aptos para compreender e assinar o termo de consentimento.
Critério de Exclusão:
1. Idade inferior a 18 anos;
2. Impossibilidade de consentir sua participação no estudo;
3. Alterações cognitivas significativas que indiquem provável quadro demencial.

Objetivo da Pesquisa:
Objetivo Primário:
Classificar a dor de pacientes distônicos.
Objetivo Secundário:
1. Realizar uma classificação e escala de dor em pacientes distônicos;2.Realizar uma avaliação de sintomas não-motores (psiquiátricos, cognitivos,
sono, autonômicos) na distonia.

Avaliação dos Riscos e Benefícios:
Riscos:
Risco de constrangimento durante a entrevista.
Benefícios:
Permitir a criação de uma escala para avaliação da dor específica para pacientes portadores de distonia.

Comentários e Considerações sobre a Pesquisa:
Trata-se de pesquisa clínica do serviço de Neurologia do HGF e da HC-FMUSP, onde o HGf é uma instituição participante,com coleta de dados 01/07/2021 à 31/03/2022 e planejamento para conclusão do estudo em 30/12/22

Considerações sobre os Termos de apresentação obrigatória:

Descrita no Parecer 4.581.856.

Conclusões ou Pendências e Lista de Inadequações:

Projeto aprovado. Pesquisadora atendeu todas as pendências.

Considerações Finais a critério do CEP:

De acordo com a Resolução CNS nº 466/2012, item XI.2, cabe ao pesquisador “elaborar e apresentar os relatórios parciais e final”.

Dessa forma, solicitamos ao pesquisador responsável que enviem os relatórios parciais(semestralmente) e o reltóiro final por meio de notificação na Plataforma Brasil.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1695957.pdf	12/05/2021 12:14:11		Aceito
Projeto Detalhado / Brochura Investigador	Projeto_Distonia_FlaviaRolim.docx	12/05/2021 12:13:52	Flávia de Paiva Santos Rolim	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_DISTONIA_PADRAO_2021.docx	12/05/2021 11:58:23	Flávia de Paiva Santos Rolim	Aceito
Folha de Rosto	Folhaderosto_SEAP_distonia.pdf	12/02/2021 14:38:52	Flávia de Paiva Santos Rolim	Aceito
Declaração de Pesquisadores	termo_compromisso_pesquisador.JPG	05/02/2021 09:08:54	Flávia de Paiva Santos Rolim	Aceito
Declaração de Instituição e Infraestrutura	infraestrutura.JPG	05/02/2021 09:08:21	Flávia de Paiva Santos Rolim	Aceito
Outros	fiel_depositario.pdf	29/01/2021 11:28:31	Flávia de Paiva Santos Rolim	Aceito
Declaração de concordância	autorizacao_chefeservico.pdf	29/01/2021 11:28:01	Flávia de Paiva Santos Rolim	Aceito

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

FORTALEZA, 18 de Maio de 2021

Assinado por:
PATRICIA QUIRINO DA COSTA
(Coordenador(a))

Endereço: Rua Avila Goulart, nº 900 Sala localizada e identificada, piso térreo do HGF, entrada pela portaria lateral do
Bairro: Papicu **CEP:** 60.191-070
UF: CE **Município:** FORTALEZA
Telefone: (85)3101-7078 **E-mail:** cephgf.ce@gmail.com

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Classificação de dor e sintomas não-motores em pacientes distônicos.
Pesquisador: SARAH TEIXEIRA CAMARGOS
Área Temática:
Versão: 2
CAAE: 31832920.2.2003.5149
Instituição Proponente: Hospital das Clínicas - Universidade Federal de Minas Gerais
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 5.698.084

Apresentação do Projeto:
Este estudo envolve indivíduos com diagnóstico de distonia de qualquer etiologia (adquirida, hereditária ou idiopática) e de qualquer distribuição (focal, segmentar, multifocal, generalizada, hemidistonia). É um estudo transversal para avaliar de dor e outros sintomas não-motores nas distonias, no qual a maioria dos pacientes será avaliado apenas uma única vez. A outra parte dos pacientes (40) será avaliada até duas vezes para validação da classificação – intra e inter-examinadores.
São apresentados na Plataforma Brasil (PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1624784.pdf):
"3.5 Critérios de inclusão
a) Paciente com diagnóstico clínico de distonia conforme os critérios internacionais atuais (1);
b) Pacientes maiores de 18 anos;
c) Pacientes intelectualmente aptos para compreender e assinar o termo de consentimento.
3.6 Critérios de exclusão
a) Idade inferior a 18 anos;
b) Impossibilidade de consentir sua participação no estudo;
c) Alterações cognitivas significativas que indiquem provável quadro demencial."

Objetivo da Pesquisa:
São apresentados na Plataforma Brasil (PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1624784.pdf):
"Objetivo Primário:

a) Classificar a dor de pacientes distônicos.
Objetivo Secundário:
b) Realizar uma classificação e escala de dor em pacientes distônicos;
c) Realizar uma avaliação de sintomas não-motores (psiquiátricos, cognitivos, sono, autonômicos) na distonia."

Avaliação dos Riscos e Benefícios:
São apresentados no TCLE (TCLE_distoniaSC092022.pdf):
"4 – Benefícios:
O principal objetivo deste estudo será avaliar o tipo de dor em pacientes distônicos e tentar classificá-la. Isso trará benefício para nos ajudar a entender melhor a dor que ocorre em pacientes distônicos, a fim de separá-la em tipos diferentes para que estudos futuros possam estudar melhores formas de melhor a dor na distonia.
5 – Desconfortos e riscos decorrentes da participação na pesquisa A pesquisa envolve algumas perguntas sobre o senhor e sobre os sintomas que o senhor sente. Nenhum procedimento invasivo será feito nesta pesquisa. Dessa forma, o desconforto e risco relacionados a participação no estudo estão no relato dos sintomas e fatos relacionados a doença."

Comentários e Considerações sobre a Pesquisa:
A avaliação dos pacientes e a coleta de dados serão realizadas no Ambulatório de Neurocirurgia Funcional do Instituto de Psiquiatria do HCFMUSP, no Ambulatório de Distúrbios do Movimento e em Ambulatórios de Toxina Botulínica HC-FMUSP.

Centros coparticipantes da pesquisa: HC-UFMG/EBSERH, com aprovação do GEP do HC-UFMG/EBSERH (ParecerGEP.pdf), Hospital de Clínicas - UNICAMP, Universidade Federal de São Paulo - UNIFESP/EPM, Hospital das Clínicas da Faculdade de Medicina de Ribeirão
Preto da USP - HCFMRP.

Considerações sobre os Termos de apresentação obrigatória:
cartarespostaparecer5266642.pdf: carta resposta ao CEP, referente ao Número do Parecer: 5.266.642 de 26 de Fevereiro de 2022 (PB_PARECER_CONSUBSTANCIADO_CEP_5266642.pdf). Esclarece: "Serão recrutados no HC_UFMG cerca de 20 pacientes portadores de distonia cervical. Serão colhidos os dados para a pesquisa durante a consulta do paciente no Ambulatório de Toxina Botulínica do HC-UFMG que funciona nas manhãs de sexta feira. O período de coleta será o de 8 a

10 semanas. Foi adicionado no cronograma de execução o recrutamento de pacientes, que será de 04/11/2022 a 27/01/2023".

Conclusões ou Pendências e Lista de Inadequações:

Aprova-se a pesquisa.

Considerações Finais a critério do CEP:

Tendo em vista a legislação vigente (Resolução CNS 466/12), o CEP-UFMG recomenda aos Pesquisadores: comunicar toda e qualquer alteração do projeto e do termo de consentimento via emenda na Plataforma Brasil, informar imediatamente qualquer evento adverso ocorrido durante o desenvolvimento da pesquisa (via documental encaminhada em papel), apresentar na forma de notificação relatórios parciais do andamento do mesmo a cada 06 (seis) meses e ao término da pesquisa encaminhar a este Comitê um sumário dos resultados do projeto (relatório final).

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1624784.pdf	06/09/2022 10:13:44		Aceito
Outros	cartarespostaparecer5266642.pdf	06/09/2022 10:08:02	SARAH TEIXEIRA CAMARGOS	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_distoniaSC092022.pdf	06/09/2022 10:04:24	SARAH TEIXEIRA CAMARGOS	Aceito
Outros	ParecerGEP.pdf	08/02/2022 13:31:30	SARAH TEIXEIRA CAMARGOS	Aceito
Outros	parecerclm.pdf	08/02/2022 13:29:31	SARAH TEIXEIRA CAMARGOS	Aceito
Folha de Rosto	folhaderostonova.pdf	07/02/2022 14:19:51	SARAH TEIXEIRA CAMARGOS	Aceito
Outros	u9435p857_60b4ebbab9cea_SARAH.PDF	14/06/2021 17:57:38	SARAH TEIXEIRA CAMARGOS	Aceito
Outros	Adendo_outros_centros.pdf	27/07/2020 16:44:01	Daniel Ciampia Araujo de Andrade	Aceito
Outros	carta_compromisso_doutorado.pdf	07/05/2020 19:29:15	Daniel Ciampia Araujo de Andrade	Aceito
Outros	dados_digitais.pdf	07/05/2020 19:28:48	Daniel Ciampia Araujo de Andrade	Aceito
Outros	aprovacao_departamento.pdf	07/05/2020 19:27:49	Daniel Ciampia Araujo de Andrade	Aceito
Outros	escala_sintomas_nao_motores.pdf	07/05/2020	Daniel Ciampia	Aceito

Outros	escala_sintomas_nao_motores.pdf	19:26:24	Araujo de Andrade	Aceito
Outros	Dados_Pessoais.pdf	07/05/2020 19:25:28	Daniel Ciampia Araujo de Andrade	Aceito
Outros	Classificacao.docx	07/05/2020 19:24:19	Daniel Ciampia Araujo de Andrade	Aceito
Outros	BFM.doc	07/05/2020 19:23:18	Daniel Ciampia Araujo de Andrade	Aceito
Outros	EuroQol.pdf	07/05/2020 19:23:03	Daniel Ciampia Araujo de Andrade	Aceito
Outros	Dor.pdf	07/05/2020 19:22:24	Daniel Ciampia Araujo de Andrade	Aceito
Outros	Distonia.pdf	07/05/2020 19:22:13	Daniel Ciampia Araujo de Andrade	Aceito
Outros	FAB.pdf	07/05/2020 19:21:43	Daniel Ciampia Araujo de Andrade	Aceito
Projeto Detalhado / Brochura Investigador	Projeto.docx	07/05/2020 19:16:34	Daniel Ciampia Araujo de Andrade	Aceito
Outros	Curriculo_Clarice.pdf	17/03/2020 14:39:50	Daniel Ciampia Araujo de Andrade	Aceito
Outros	Curriculo_Ciampi.pdf	17/03/2020 14:39:32	Daniel Ciampia Araujo de Andrade	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

BELO HORIZONTE, 12 de Outubro de 2022

Assinado por:
Críssia Carem Paiva Fontainha
(Coordenador(a))

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Classificação de dor e sintomas não-motores em pacientes distônicos.
Pesquisador: DENISE MARIA MENESES CURY PORTELA
Área Temática:
Versão: 1
CAAE: 31832920.2.2009.5210
Instituição Proponente: INSTITUTO DE ENSINO SUPERIOR DO PIAUI LTDA
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.791.641

Apresentação do Projeto:
Trata-se de uma emenda (V4) ao projeto "Classificação de dor e sintomas não-motres em pacientes distônicos" vinculado ao curso de Medicina. É um estudo transversal para avaliar de dor e outros sintomas não-motores nas distonias,no qual a maioria dos pacientes será avaliado apenas uma única vez. A outra parte dos pacientes (40) será avaliada até duas vezes para validação da classificação – intra e inter-examinadores. A avaliação dos pacientes e a coleta de dados serão realizadas no Ambulatório de Neurocirurgia Funcional do Instituto de Psiquiatria do HCFMUSP, no Ambulatório de Distúrbios do Movimento e em Ambulatórios de Toxina Botulínica HC-FMUSP e no Centro Integrado de Saúde Lineu Araújo em Teresina-PI.Critérios de inclusão: Paciente com diagnóstico clínico de distonia conforme os critérios internacionais atuais (1); Pacientes maiores de 18 anos; Pacientes intelectualmente aptos para compreender e assinar o termo de consentimento.

Objetivo da Pesquisa:
O objetivo da emenda é solicitar a inclusão de dois centros coparticipantes:
(1) Hospital das Clínicas Da Faculdade de Medicina de Ribeirão Preto – responsável Dra. Manuelina Mariana Capellari Macruz Brito (novo responsável); e 2) Instituto de Ensino Superior do Piauí Araújo

(nova instituição) - responsável Dra. Denise Maria Meneses Cury Portela.

Avaliação dos Riscos e Benefícios:

Sem alterações em termos de riscos e benefícios.

Comentários e Considerações sobre a Pesquisa:

Os novos centros seguirão aos mesmo protocolos, sem alteração de TCLE.

Considerações sobre os Termos de apresentação obrigatória:

Todos os termos com os novos Centros foram postados.

Recomendações:

-

Conclusões ou Pendências e Lista de Inadequações:

A emenda ao protocolo de pesquisa de pesquisa sobre a inclusão de dois novos centros participantes foi aprovada porque está elaborada de acordo com a Res. 466/12 do CNS.

Considerações Finais a critério do CEP:

O Parecer do colegiado de que a emenda ao protocolo de pesquisa está APROVADO foi acatado porque encontra-se elaborado de acordo com as recomendações éticas da Resolução 466/2012 e 510/2016 do Conselho Nacional de Saúde.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1756300.pdf	14/06/2021 12:11:09		Aceito
Outros	Declaracao_instituicao_coparticipante.pdf	10/06/2021 20:02:28	DENISE MARIA MENESES CURY PORTELA	Aceito
Outros	Termo_de_Compromisso_de_Apresentacao_de_Documentos_Obrigatorios_Assinados.pdf	10/06/2021 19:45:03	DENISE MARIA MENESES CURY PORTELA	Aceito
Declaração de Pesquisadores	Declaracao_de_compromisso_dos_Pesquisadores.pdf	10/06/2021 19:44:14	DENISE MARIA MENESES CURY PORTELA	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.pdf	10/06/2021 19:42:46	DENISE MARIA MENESES CURY PORTELA	Aceito

Endereço: Rua Vitorino Orthiges Fernandes, 6123
Bairro: Bairro do Uruguai **CEP:** 64.073-505
UF: PI **Município:** TERESINA
Telefone: (86)2106-0738 **Fax:** (86)2106-0740 **E-mail:** cep@uninovafapi.edu.br

Cronograma	Cronograma.pdf	10/06/2021 19:42:16	DENISE MARIA MENESES CURY PORTELA	Aceito
Orçamento	Orcamento.pdf	10/06/2021 19:41:50	DENISE MARIA MENESES CURY PORTELA	Aceito
Folha de Rosto	Folha_de_rosto_novafapi.pdf	10/06/2021 19:41:30	DENISE MARIA MENESES CURY PORTELA	Aceito
Outros	ADENDO_NOVOS_CENTROS_E3.pdf	15/04/2021 21:12:08	Daniel Ciampia Araujo de Andrade	Aceito
Outros	ADENDO_NOVOS_CENTROS_E2.pdf	25/01/2021 14:50:55	Daniel Ciampia Araujo de Andrade	Aceito
Outros	Adendo_outros_centros.pdf	27/07/2020 16:44:01	Daniel Ciampia Araujo de Andrade	Aceito
Outros	carta_compromisso_doutorado.pdf	07/05/2020 19:29:15	Daniel Ciampia Araujo de Andrade	Aceito
Outros	dados_digitais.pdf	07/05/2020 19:28:48	Daniel Ciampia Araujo de Andrade	Aceito
Outros	aprovacao_departamento.pdf	07/05/2020 19:27:49	Daniel Ciampia Araujo de Andrade	Aceito
Outros	escala_sintomas_nao_motores.pdf	07/05/2020 19:26:24	Daniel Ciampia Araujo de Andrade	Aceito
Outros	Dados_Pessoais.pdf	07/05/2020 19:25:28	Daniel Ciampia Araujo de Andrade	Aceito
Outros	Classificacao.docx	07/05/2020 19:24:19	Daniel Ciampia Araujo de Andrade	Aceito
Outros	BFM.doc	07/05/2020 19:23:18	Daniel Ciampia Araujo de Andrade	Aceito
Outros	EuroQol.pdf	07/05/2020 19:23:03	Daniel Ciampia Araujo de Andrade	Aceito
Outros	Dor.pdf	07/05/2020 19:22:24	Daniel Ciampia Araujo de Andrade	Aceito
Outros	Distonia.pdf	07/05/2020 19:22:13	Daniel Ciampia Araujo de Andrade	Aceito
Outros	FAB.pdf	07/05/2020 19:21:43	Daniel Ciampia Araujo de Andrade	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_atual.docx	07/05/2020 19:16:53	Daniel Ciampia Araujo de Andrade	Aceito
Projeto Detalhado / Brochura Investigador	Projeto.docx	07/05/2020 19:16:34	Daniel Ciampia Araujo de Andrade	Aceito
Outros	Curriculo_Clarice.pdf	17/03/2020	Daniel Ciampia	Aceito

Outros	Curriculo_Clarice.pdf	14:39:50	Araujo de Andrade	Aceito
Outros	Curriculo_Ciampi.pdf	17/03/2020 14:39:32	Daniel Ciampia Araujo de Andrade	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

TERESINA, 18 de Junho de 2021

Assinado por:
FRANCISCA TEREZA COELHO MATOS
(Coordenador(a))

UNIFESP

UNIVERSIDADE FEDERAL DE SÃO PAULO

1933

Comitê de Ensino, Pesquisa e Extensão - CoEPE

Hospital São Paulo-Hospital Universitário

UNIFESP

Ofício CoEPE do HSP-HU/UNIFESP nº 549/20

São Paulo, 13 de novembro de 2020.

Ilmo(a). Sr(a).

Prof(a). Dr(a). Henrique Ballalai Ferraz

Orientador(a).

Prezado(a) Professor (a)

O Comitê de Ensino e Pesquisa e Extensão do Hospital São Paulo-HU da UNIFESP, está de acordo com a realização do Projeto de Pesquisa intitulada: **"Classificação de dor e sintomas não motores em pacientes com distonia",** da aluna de especialização, Graziele Costa Santos.

Atenciosamente,

Reinaldo Salomão

Prof. Dr. Reinaldo Salomão

Coordenador do Comitê de Ensino, Pesquisa e Extensão

Hospital São Paulo – Hospital Universitário da Unifesp

Rua Napoleão de Barros, 715 1º andar – CEP: 04024-002 – São Paulo – SP

Tel.: (55) (11) 5576-4848 vop 17253

APPENDIX E — Patient consent form.

HOSPITAL DAS CLÍNICAS DA UFMG

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

DADOS DA PESQUISA

Título da pesquisa – Classificação de dor e sintomas não-motores em pacientes distônicos.

Prezado Sr. (a), Você está sendo convidado a participar da pesquisa **"Classificação de dor e sintomas não-motores em pacientes distônicos."**

1 – Justificativa e Objetivos:

O principal objetivo deste estudo será avaliar a dor e outro aspectos não motores como qualidade de vida, sintomas psiquiátricos e autonômicos em pacientes com distonia.

Serão estudados pacientes distônicos de várias causas diferentes para avaliar esses sintomas importantes com especial atenção a sintomas dolorosos, pois são sintomas ainda pouco estudados na Distonia, apesar de ter um grande impacto no dia a dia do paciente. Buscamos classificar os diferentes tipos de dor para entender melhor o tipo de dor mais importante em pacientes distônicos.

2 – Descrição dos procedimentos que serão realizados, com seus propósitos.

Para esta pesquisa o/a Sr(a) terá que realizar inicialmente uma consulta médica com história e exame físico completos. Nesta consulta serão aplicado questionários de dor, para podermos medir o nível de dor e entender o tipo de dor que o senhor tem, além de questionários em relação a qualidade de vida e sintomas como ansiedade e depressão. De acordo com um sorteio o senhor será avaliado uma única vez ou duas vezes com as mesmas perguntas.

3 – Avaliações e descrição dos procedimentos realizados

O senhor será avaliado uma ou duas vezes no dia em que vier a sua consulta médica. A avaliação consiste em perguntas sobre os seus sintomas da distonia (quando começou, onde apresenta os sintomas e assim por diante), exame físico para avaliar os sintomas de distonia e aplicação de alguns questionários de perguntas sobre dor, qualidade de vida, ansiedade/depressão e outros sintomas possivelmente relacionados a distonia.

4 – Benefícios:

O principal objetivo deste estudo será avaliar o tipo de dor em pacientes distônicos e tentar classificá-la. Isso trará benefício para nos ajudar a entender melhor a dor que ocorre em pacientes

distônicos, a fim de separá-la em tipos diferentes para que estudos futuros possam estudar melhores formas de melhor a dor na distonia.

5 – Desconfortos e riscos decorrentes da participação na pesquisa

A pesquisa envolve algumas perguntas sobre o senhor e sobre os sintomas que o senhor sente. Nenhum procedimento invasivo será feito nesta pesquisa. Dessa forma, o desconforto e risco relacionados a participação no estudo estão no relato dos sintomas e fatos relacionados a doença.

6 – Forma de acompanhamento e assistência

O senhor será avaliado após a sua consulta de rotina no ambulatório que o senhor já faz parte. Sendo este estudo uma avaliação única ou, em alguns casos, dupla, porém feito na mesma consulta e não interfere no acompanhamento habitual do senhor que será mantido.

7 – Garantia de acesso

Em qualquer etapa do estudo, incluindo após o término ou caso interrupção, o/a Sr(a) terá acesso aos profissionais responsáveis pela pesquisa para esclarecimento de eventuais dúvidas.

8 – É garantida a liberdade da retirada da pesquisa a qualquer momento, ou se recursar a participar do estudo, sem qualquer prejuízo à continuidade de seu tratamento na Instituição;

9 – O/A Sr(a) tem direito de confidencialidade – As informações obtidas serão analisadas em conjunto com outros pacientes, não sendo divulgada a identificação de nenhum paciente;

10 – É seu direito de ser mantido atualizado sobre os resultados parciais das pesquisas, quando em estudos abertos, ou de resultados que sejam do conhecimento dos pesquisadores;

11 – Despesas e compensações:

Não há despesas pessoais para o participante em qualquer fase do estudo, incluindo exames e consultas. Também não há compensação financeira relacionada à sua participação. O participante poderá buscar indenização em caso de danos provenientes da pesquisa

12 - Compromisso do pesquisador de utilizar os dados e o material coletado somente para esta pesquisa.

13 - Garantia de que o/a Sr(a) receberá uma via do termo de consentimento

Em qualquer etapa do estudo, você terá acesso aos profissionais responsáveis pela pesquisa para esclarecimento de dúvidas. O principal investigador é o Dra. Sarah Teixeira Camargos poderá ser encontrada no endereço Alameda Alvaro Celso 175, sexto andar . Belo Horizonte, Minas Gerais. O telefone é (31)3307-9540. O email sarahcamargos@ufmg.br.

Outra maneira de satisfazer suas dúvidas quanto a esse estudo é entrar em contato com o nosso Comitê de Ética em Pesquisa da UFMG. Trata-se de um setor que tem a finalidade de proteger o participante de qualquer risco envolvendo pesquisas, além de esclarecer qualquer dúvida sobre a sua participação.O contato pode ser feito pelos meios abaixo: Comitê de ética em pesquisa da UFMG, tel (31) 3409-4592 ; email: coep@prpq.ufmg.br

AV. Presidente Antônio Carlos, 6627, Pampulha - Belo Horizonte - MG - CEP 31270-901 Unidade Administrativa II - 2º Andar - Sala: 2005. (Horário de atendimento: 09:00 às 11:00 / 14:00 às 16:00).

Fui suficientemente informado a respeito do estudo “Classificação de dor e sintomas não motores em pacientes distônicos”.

Eu discuti as informações acima com o Pesquisador Responsável (Dra. Sarah Teixeira Camargos) ou pessoa (s) por ele delegada (s) sobre a minha decisão em participar nesse estudo. Ficaram claros para mim os objetivos, os procedimentos, os potenciais desconfortos e riscos e as garantias. Concordo voluntariamente em participar deste estudo, assino este termo de consentimento e recebo uma via rubricada pelo pesquisador

Este termo será assinado em 02 (duas) vias, uma ficará com o participante.

Belo Horizonte, ____ de _____de 20___

Nome do participante:

_____ _____

Assinatura do participante ou representante legal Data

Eu, Sarah Teixeira Camargos, comprometo-me a cumprir todas as exigências e responsabilidades a mim conferidas neste termo e na resolução 466/12.

_____ _____

Assinatura da pesquisadora Data

APPENDIX F — Published article “Pain in dystonia: development and validation of the Dystonia Pain Classification System (Dystonia-PCS).”

RESEARCH ARTICLE

Development and Validation of the Dystonia-Pain Classification System: A Multicenter Study

Clarice Listik, MD, MSc,[1] Eduardo Listik, MSc, PhD,[2] Flávia de Paiva Santos Rolim, MD, MSc,[3] Denise Maria Meneses Cury Portela, MD, MSc,[4] Santiago Perez Lloret, MD, PhD,[5,6] Natália Rebeca de Alves Araújo,[4] Pedro Rubens Araújo Carvalho, MD,[3] Graziele Costa Santos, MD,[7] João Carlos Papaterra Limongi, MD, PhD,[1] Francisco Cardoso, MD, MSc, PhD,[8] Veit Mylius, MD,[9,10] Florian Brugger, MD,[11] Ana Mercia Fernandes, MSc,[1] Egberto Reis Barbosa, MD, MSc, PhD,[1] Manoel Jacobsen Teixeira, MD, MSc, PhD,[1] Henrique Ballalai Ferraz, MD, MSc, PhD,[7] Sarah Teixeira Camargos, MD, MSc, PhD,[8] Pain in Dystonia Study Group, Rubens Gisbert Cury, MD, PhD,[1] and Daniel de Ciampi de Andrade, MD, PhD[1,12*]

[1]*Department of Neurology, Movement Disorders Center, School of Medicine, University of São Paulo, São Paulo, Brazil*
[2]*Department of Neurology, University of Alabama at Birmingham, Birmingham, Alabama, USA*
[3]*Department of Neurology, Hospital Geral de Fortaleza, Fortaleza, Brazil*
[4]*Department of Neurology, Instituto de Ensino Superior do Piaui, Teresina, Brazil*
[5]*Observatorio de Salud Pública, Pontificia Universidad Católica Argentina, Buenos Aires, Argentina*
[6]*Department of Physiology, Faculty of Medicine, University of Buenos Aires, Buenos Aires, Argentina*
[7]*Department of Neurology, Universidade Federal de Sao Paulo (UNIFESP), São Paulo, Brazil*
[8]*Department of Neurology, Hospital das Clínicas da Universidade Federal de Minas Gerais, Belo Horizonte, Brazil*
[9]*Department of Neurology, Center for Neurorehabilitation, Valens, Switzerland*
[10]*Department of Neurology, Philipps University, Marburg, Germany*
[11]*Department of Neurology, Kantonsspital St. Gallen, St. Gallen, Switzerland*
[12]*Department of Health Science and Technology, Center for Neuroplasticity and Pain (CNAP), Faculty of Medicine, Aalborg University, Aalborg, Denmark*

ABSTRACT: Background: Dystonia is associated with disabling nonmotor symptoms like chronic pain (CP), which is prevalent in dystonia and significantly impacts the quality of life (QoL). There is no validated tool for assessing CP in dystonia, which substantially hampers pain management.
Objective: The aim was to develop a CP classification and scoring system for dystonia.
Methods: A multidisciplinary group was established to develop the Dystonia-Pain Classification System (Dystonia-PCS). The classification of CP as related or unrelated to dystonia was followed by the assessment of pain severity score, encompassing pain intensity, frequency, and impact on daily living. Then, consecutive patients with inherited/idiopathic dystonia of different spatial distribution were recruited in a cross-sectional multicenter validation study. Dystonia-PCS was compared to validated pain, mood, QoL, and dystonia scales (Brief Pain Inventory, Douleur Neuropathique-4 questionnaire, European QoL-5 Dimensions-3 Level Version, and Burke–Fahn–Marsden Dystonia Rating Scale).
Results: CP was present in 81 of 123 recruited patients, being directly related to dystonia in 82.7%, aggravated by dystonia in 8.8%, and nonrelated to dystonia in 7.5%. Dystonia-PCS had excellent intra-rater (Intraclass Correlation Coefficient - ICC: 0.941) and inter-rater (ICC: 0.867) reliability. In addition, pain severity score correlated with European QoL-5 Dimensions-3 Level Version's pain subscore ($r = 0.635$, $P < 0.001$) and the Brief Pain Inventory's severity and interference scores ($r = 0.553$, $P < 0.001$ and $r = 0.609$, $P < 0.001$, respectively).
Conclusions: Dystonia-PCS is a reliable tool to categorize and quantify CP impact in dystonia and will help improve clinical trial design and management of CP in patients

*__Correspondence to:__ Dr. Daniel Ciampi de Andrade, Department of Health Science and Technology, Centre for Neuroplasticity and Pain (CNAP), Faculty of Medicine, Aalborg University, Room 12.02.018, Selma Lagerløfs Vej 249, 9260 Gistrup, Denmark; E-mail: dca@hst.aau.dk

Members of the Pain in Dystonia Study Group are listed in the Appendix.

Relevant conflicts of interest/financial disclosures: None.

Funding agencies: The Pain Center–HC-FMUSP. M.J.T. and D.C.A. are funded by CNPq (scientific production scholarship by Conselho Nacional de Pesquisa). The Center for Neuroplasticity and Pain is supported by the Danish National Research Foundation (DNRF121). D.C.A. is supported by Novo Nordisk Grant NNF21OC0072828.

Received: 22 February 2023; **Revised:** 4 April 2023; **Accepted:** 10 April 2023

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29423

APPENDIX G — Published article “Abnormal sensory thresholds of dystonic patients are not affected by deep brain stimulation.”

DOI: 10.1002/ejp.1757

ORIGINAL ARTICLE

EJP European Journal of Pain

Abnormal sensory thresholds of dystonic patients are not affected by deep brain stimulation

Clarice Listik[1] | **Rubens Gisbert Cury**[1] | **Valquiria Aparecida da Silva**[2] | **Sara Carvalho Barbosa Casagrande**[1] | **Eduardo Listik**[3] | **Naira Link**[2] | **Ricardo Galhardoni**[2,4,5] | **Egberto Reis Barbosa**[1] | **Manoel Jacobsen Teixeira**[2] | **Daniel Ciampi de Andrade**[1,2,6]

[1]Movement Disorders Center, Department of Neurology, School of Medicine, University of São Paulo, São Paulo, SP, Brazil

[2]Pain Center, Neurosurgery Division, Department of Neurology, School of Medicine, University of São Paulo, São Paulo, SP, Brazil

[3]Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, USA

[4]Federal University of ABC, São Bernardo do Campo, SP, Brazil

[5]School of Medicine, Santo André, SP, Brazil

[6]Pain Center, Instituto do Cancer do Estado de São Paulo, São Paulo, SP, Brazil

Correspondence
Daniel Ciampi de Andrade, Av. Dr. Enéas de Carvalho Aguiar, 255, 5° andar, sala 5084 – Cerqueira César 05403-900 São Paulo, SP, Brazil.
Email: ciampi@usp.br

Abstract

Background: Unlike motor symptoms, the effects of deep brain stimulation (DBS) on non-motor symptoms associated with dystonia remain unknown.

Methods: The objective of this study was to assess the effects of DBS on evoked experimental pain and cutaneous sensory thresholds in a crossover, double-blind on/off study and compare these results with those of healthy volunteers (HV).

Results: Sixteen patients with idiopathic dystonia (39.9 ± 13 years old, $n = 14$ generalized) with DBS of the globus pallidus internus underwent a battery of quantitative sensory testing and assessment using a pain top-down modulation system (conditioned pain modulation, CPM). Results for the more and less dystonic body regions were compared in on and off stimulation. The patients' results were compared to age- and sex-matched HV. Descending pain modulation CPM responses in dystonic patients (on-DBS, 11.8 ± 40.7; off-DBS, 1.8 ± 22.1) was abnormally low (defective) compared to HV (−15.6 ± 23.5, respectively $p = .006$ and $p = .042$). Cold pain threshold and cold hyperalgesia were 54.8% and 95.7% higher in dystonic patients compared to HV. On-DBS CPM correlated with higher Burke-Fahn-Marsden disability score ($r = 0.598$; $p = .014$). While sensory and pain thresholds were not affected by DBS on/off condition, pain modulation was abnormal in dystonic patients and tended to be aggravated by DBS.

Conclusion: The analgesic effects after DBS do not seem to depend on short-duration changes in cutaneous sensory thresholds in dystonic patients and may be related to changes in the central processing of nociceptive inputs.

Significance

The sensory and pain thresholds were not affected by deep brain stimulation (DBS) on/off condition, but pain modulation was abnormal in dystonic patients. The analgesic effects seen after DBS do not seem to depend on short-duration changes

Abbreviations: BFM, Burke-Fahn-Marsden; BPI, brief pain inventory; CDT, cold detection threshold; CPM, conditioned pain modulation; CPT, cold pain threshold; C-TS, conditioned test stimulus; DBS, deep brain stimulation; DN4, Douleur neuropathique-4; FAB, frontal assessment battery; GPi, globus pallidus internus; HADS, Hospital Anxiety and Depression scale; HPT, heat pain threshold; HV, healthy volunteers; McGill, short-form McGill pain questionnaire; MDT, mechanical detection threshold; MH, mechanical hyperalgesia; MPT, mechanical pain threshold; NMS, non-motor symptoms; NPSI, Neuropathic Pain Symptom Inventory; PD, Parkinson's disease; QoL, quality of life; QST, quantitative sensory testing; SF-12, SF-12 quality of life questionnaire; SuC, pain rating to suprathreshold cold stimulation; SuH, pain rating to suprathreshold heat stimulation; TS, test stimulus; U-TS, unconditioned test stimulus; VAS, visual analogue scale; VDT, vibration detection threshold; WDT, warm detection threshold.

APPENDIX H — Published article “Improvement of Non-motor Symptoms and Quality of Life After Deep Brain Stimulation for Refractory Dystonia: A 1-Year Follow-Up.”

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 04 October 2021
doi: 10.3389/fneur.2021.717239

Improvement of Non-motor Symptoms and Quality of Life After Deep Brain Stimulation for Refractory Dystonia: A 1-Year Follow-Up

*Clarice Listik[1], Rubens Gisbert Cury[1], Sara Carvalho Barbosa Casagrande[1], Eduardo Listik[2], Debora Arnaut[1], Natally Santiago[1], Valquiria Aparecida Da Silva[1], Ricardo Galhardoni[1], Júlia de Lima Arantes Machado[1], Jessica Campelo de Almeida[1], Egberto Reis Barbosa[1], Manoel Jacobsen Teixeira[1] and Daniel Ciampi De Andrade[1]**

[1] Department of Neurology, School of Medicine, University of São Paulo, São Paulo, Brazil, [2] Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, United States

Introduction: Deep brain stimulation (DBS) is a treatment option for refractory dystonia's motor symptoms, while its non-motor symptoms (NMS) have been less systematically assessed. We aimed to describe the effects of DBS on NMS in refractory generalized inherited/idiopathic dystonia prospectively.

Methods: We evaluated patients before and 1 year after DBS surgery and applied the following scales: Burke–Fahn–Marsden Rating Scale (BFMRS), NMS Scale for Parkinson's Disease (NMSS-PD), Parkinson's Disease Questionnaire-8, short-form Brief Pain Inventory (BPI), Neuropathic Pain Symptom Inventory (NPSI), and short-form McGill Pain Questionnaire (MPQ).

Results: Eleven patients (38.35 ± 11.30 years) underwent surgery, all with generalized dystonia. Motor BFMRS subscore was 64.36 ± 22.94 at baseline and 33.55 ± 17.44 1 year after DBS surgery (47.9% improvement, $p = 0.003$). NMSS-PD had a significant change 12 months after DBS, from 70.91 ± 59.07 to 37.18 ± 55.05 (47.5% improvement, $p = 0.013$). NMS changes were mainly driven by changes in the gastrointestinal ($p = 0.041$) and miscellaneous domains ($p = 0.012$). Seven patients reported chronic pain before DBS and four after it. BPI's severity and interference scores were 4.61 ± 2.84 and 4.12 ± 2.67, respectively, before surgery, and 2.79 ± 2.31 (0.00–6.25) and 1.12 ± 1.32 (0.00–3.00) after, reflecting a significant improvement ($p = 0.043$ and $p = 0.028$, respectively). NPSI score was 15.29 ± 13.94 before, while it was reduced to 2.29 ± 2.98 afterward ($p = 0.028$). MPQ's total score was 9.00 ± 3.32 before DBS, achieving 2.71 ± 2.93 after ($p = 0.028$).

Conclusions: DBS improves NMS in generalized inherited/idiopathic dystonia, including chronic pain.

Keywords: dystonia, deep brain stimulation, non-motor symptoms, pain, quality of life

OPEN ACCESS

Edited by:
Huifang Shang, Sichuan University, China

Reviewed by:
Carlos Henrique Ferreira Camargo, Federal University of Paraná, Brazil
Leonor Correia Guedes, Centro Hospitalar Lisboa Norte (CHLN), Portugal

****Correspondence:***
Daniel Ciampi De Andrade
ciampi@usp.br

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *30 May 2021*
Accepted: *01 September 2021*
Published: *04 October 2021*

Citation:
Listik C, Cury RG, Casagrande SCB, Listik E, Arnaut D, Santiago N, Da Silva VA, Galhardoni R, Machado JdLA, Almeida JCd, Barbosa ER, Teixeira MJ and De Andrade DC (2021) Improvement of Non-motor Symptoms and Quality of Life After Deep Brain Stimulation for Refractory Dystonia: A 1-Year Follow-Up. Front. Neurol. 12:717239. doi: 10.3389/fneur.2021.717239

HIGHLIGHTS

- DBS improves non-motor symptoms in generalized inherited/idiopathic dystonia.
- Chronic pain is improved after DBS in generalized inherited/idiopathic dystonia.
- Quality of life improvement was driven by the non-motor symptoms' improvement.

APPENDIX I — Published article “Exploring clinical outcomes in patients with idiopathic/inherited isolated generalized dystonia and stimulation of subthalamic region.”

Exploring clinical outcomes in patients with idiopathic/inherited isolated generalized dystonia and stimulation of the subthalamic region

Explorando os desfechos clínicos em pacientes com distonia idiopática/hereditária generalizada isolada submetidos a estimulação da região subtalâmica

Clarice Listik[1] Jorge Dornellys Lapa[2] Sara Carvalho Barbosa Casagrande[1] Egberto Reis Barbosa[1] Ricardo Iglesio[2] Fabio Godinho[2] Kleber Paiva Duarte[2] Manoel Jacobsen Teixeira[2] Rubens Gisbert Cury[1]

[1] Universidade de São Paulo, Center for Movement Disorders, Faculty of Medicine, Department of Neurology, São Paulo SP, Brazil.
[2] Universidade de São Paulo, Faculty of Medicine, Neurosurgery Division, Departament of de Neurology, São Paulo SP, Brazil.

Address for correspondence Clarice Listik (email: clarice.listik@gmail.com).

Arq. Neuropsiquiatr. 2023;81(3):263–270.

Abstract

Background Deep Brain Stimulation (DBS) is an established treatment option for refractory dystonia, but the improvement among the patients is variable.

Objective To describe the outcomes of DBS of the subthalamic region (STN) in dystonic patients and to determine whether the volume of tissue activated (VTA) inside the STN or the structural connectivity between the area stimulated and different regions of the brain are associated with dystonia improvement.

Methods The response to DBS was measured by the Burke-Fahn-Marsden Dystonia Rating Scale (BFM) before and 7 months after surgery in patients with generalized isolated dystonia of inherited/idiopathic etiology. The sum of the two overlapping STN volumes from both hemispheres was correlated with the change in BFM scores to assess whether the area stimulated inside the STN affects the clinical outcome. Structural connectivity estimates between the VTA (of each patient) and different brain regions were computed using a normative connectome taken from healthy subjects.

Results Five patients were included. The baseline BFM motor and disability subscores were 78.30 ± 13.55 (62.00–98.00) and 20.60 ± 7.80 (13.00–32.00), respectively. Patients improved dystonic symptoms, though differently. No relationships were found between the VTA inside the STN and the BFM improvement after surgery

Keywords
- Deep Brain Stimulation
- Dystonia
- Cerebellum
- Subthalamic Nucleus
- Connectome

received
May 7, 2022
received in its final form
November 5, 2022
accepted
November 10, 2022

DOI https://doi.org/10.1055/s-0043-1764416.
ISSN 0004-282X.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

APPENDIX J — Published article “Should the Globus Pallidus Targeting Be Refined in Dystonia?”

Should the Globus Pallidus Targeting Be Refined in Dystonia?

Jorge Dornellys da Silva Lapa[1,2] Fábio Luiz Franceschi Godinho[2] Manoel Jacobsen Teixeira[3] Clarice Listik[4] Ricardo Ferrareto Iglesio[2] Kleber Paiva Duarte[2] Rubens Gisbert Cury[4]

[1] Neurosurgery Unit, Fundação de Beneficiência Hospital de Cirurgia, Cirurgia, Aracaju, Sergipe, Brazil
[2] Division of Functional Neurosurgery, Department of Neurology, University of São Paulo, School of Medicine, Sao Paulo, São Paulo, Brazil
[3] Department of Neurosurgery, University of São Paulo, São Paulo, São Paulo, Brazil
[4] Movement Disorders Center, Department of Neurology, School of Medicine, University of Sao Paulo, Sao Paulo, São Paulo, Brazil

Address for correspondence Jorge Dornellys da Silva Lapa, MD, Address: Street Roque José de Souza, 116, district Centro, 49520-000-Campo Do Brito, SE, Brazil (e-mail: dr.dornellys@hotmail.com).

J Neurol Surg A Cent Eur Neurosurg

Abstract

Background and Study Aims Deep brain stimulation (DBS) of the globus pallidus internus (GPi) is a highly effective therapy for primary generalized and focal dystonias, but therapeutic success is compromised by a nonresponder rate of up to 20%. Variability in electrode placement and in tissue stimulated inside the GPi may explain in part different outcomes among patients. Refinement of the target within the pallidal area could be helpful for surgery planning and clinical outcomes. The objective of this study was to discuss current and potential methodological (somatotopy, neuroimaging, and neurophysiology) aspects that might assist neurosurgical targeting of the GPi, aiming to treat generalized or focal dystonia.

Methods We selected published studies by searching electronic databases and scanning the reference lists for articles that examined the anatomical and electrophysiologic aspects of the GPi in patients with idiopathic/inherited dystonia who underwent functional neurosurgical procedures.

Results The sensorimotor sector of the GPi was the best target to treat dystonic symptoms, and was localized at its lateral posteroventral portion. The effective volume of tissue activated (VTA) to treat dystonia had a mean volume of 153 mm^3 in the posterior GPi area. Initial tractography studies evaluated the close relation between the electrode localization and pallidothalamic tract to control dystonic symptoms.

Regarding the somatotopy, the more ventral, lateral, and posterior areas of the GPi are associated with orofacial and cervical representation. In contrast, the more dorsal, medial, and anterior areas are associated with the lower limbs; between those areas, there is the representation of the upper limb. Excessive pallidal synchronization has a peak at the theta band of 3 to 8 Hz, which might be responsible for generating dystonic symptoms.

Conclusions Somatotopy assessment of posteroventral GPi contributes to target-specific GPi sectors related to segmental body symptoms. Tractography delineates GPi output pathways that might guide electrode implants, and electrophysiology might assist in pointing out areas of excessive theta synchronization. Finally, the identification of oscillatory electrophysiologic features that correlate with symptoms might enable closed-loop approaches in the future.

Keywords
- deep brain stimulation
- dystonia
- globus pallidus internus
- somatotopy
- hot spot

received
October 14, 2020
accepted after revision
March 9, 2021

Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/s-0041-1735856.
ISSN 2193-6315.

APPENDIX K — Published article “Rescue Subthalamic Deep Brain Stimulation for Refractory Meige Syndrome.”

Stereotactic and Functional Neurosurgery

Images in Stereotactic and Functional Neurosurgery

Stereotact Funct Neurosurg
DOI: 10.1159/000515722

Received: November 4, 2020
Accepted: March 5, 2021
Published online: April 23, 2021

Rescue Subthalamic Deep Brain Stimulation for Refractory Meige Syndrome

Veronica Tavares Aragão[a] Sara Carvalho Barbosa Casagrande[a] Clarice Listik[a]
Manoel Jacobsen Teixeira[b] Egberto Reis Barbosa[a] Rubens Gisbert Cury[a]

[a]Department of Neurology, Movement Disorders Center, School of Medicine, University of São Paulo, São Paulo, Brazil;
[b]Neurosurgery Division, Department of Neurology, School of Medicine, University of São Paulo, São Paulo, Brazil

Keywords
Dystonia · Meige syndrome · Stimulation · Rescue deep brain stimulation

Abstract
Meige syndrome is a segmental form of dystonia. It is a disabling disease, especially when refractory to treatment with botulinum toxin. A well-established therapeutic option is deep brain stimulation (DBS), and the target in bilateral globus pallidus internus (GPi DBS) demonstrated satisfactory short- and long-term efficacy. However, some patients present minor or suboptimal responses after GPi DBS, and in those cases, rescue DBS may be appropriate. The present case illustrates a good outcome after subthalamic nucleus (STN) and not after GPi DBS (considering that both were well positioned and had adequate programming). The larger dimension of the GPi and its somatotopic organization, with the stimulation outside the "face region," could explain our outcomes.

Introduction

Meige syndrome is a segmental form of dystonia composed of blepharospasm and facial/oromandibular and cervical dystonia. It is a disabling disease, especially when refractory to treatment with botulinum toxin. In such cases, a well-established therapeutic option is deep brain stimulation (DBS). Bilateral globus pallidus internus (GPi DBS) demonstrated satisfactory short- and long-term efficacy in the treatment of Meige syndrome and could serve as an effective and safe option. However, some patients present minor or suboptimal responses after GPi DBS, and in those cases, rescue DBS may be appropriate. Here, we present a patient with refractory Meige syndrome that significantly improved symptoms after a rescue subthalamic nucleus DBS (STN DBS) following failure of GPi DBS.

Case Report

A 65-year-old man presented with progressive blepharospasm, oromandibular, and cervical dystonia he was 46 years old. Initially, the treatment with botulinum toxin was partially successful, but the condition deteriorated over the years to a point in which incapacitating and prolonged blepharospasm was present throughout the day (see online suppl. Video 1; for all online suppl. material, see www.karger.com/doi/10.1159/000515722 – baseline).

Multiple oral medications were tried, such as anticholinergics, benzodiazepines, and baclofen without satisfactory improvement. Therefore, he consented to bilateral GPi DBS (Medtronic 3389 Minneapolis, MN, USA) in 2013. A stereotactic procedure is made to implant the elec-

Veronica Tavares Aragão and Sara Carvalho Barbosa Casagrande contributed equally.

karger@karger.com
www.karger.com/sfn

Correspondence to:
Rubens Gisbert Cury, rubens_cury@usp.br

APPENDIX L — Published article “Posterior-superior insular deep transcranial magnetic stimulation alleviates peripheral neuropathic pain - A pilot double-blind, randomized cross-over study.”

Neurophysiologie Clinique/Clinical Neurophysiology 51 (2021) 291—302

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

ORIGINAL ARTICLE

Posterior-superior insular deep transcranial magnetic stimulation alleviates peripheral neuropathic pain — A pilot double-blind, randomized cross-over study

Liu Dongyang[a], Ana Mércia Fernandes[a], Pedro Henrique Martins da Cunha[a], Raissa Tibes[a], João Sato[a], Clarice Listik[a], Camila Dale[a], Gabriel Taricani Kubota[a], Ricardo Galhardoni[a], Manoel Jacobsen Teixeira[a], Valquíria Aparecida da Silva[a], Jefferson Rosi[a], Daniel Ciampi de Andrade[a,b,*]

[a] *LIM-62, Pain Center, Department of Neurology, University of São Paulo, Av. Dr. Enéas de Carvalho Aguiar, 255, 5th Floor, P.O. Box: 05403-900, São Paulo, SP, Brazil*
[b] *Pain Center Instituto do Câncer Octavio Frias de Oliveira, University of São Paulo, Avenida Dr. Arnaldo 251, P.O. Box: 01246-000, São Paulo, SP, Brazil*

Received 27 April 2021; accepted 9 June 2021
Available online 24 June 2021

KEYWORDS
Insula;
Neuropathic pain;
Neuronavigation;
Peripheral neuropathy;
Transcranial magnetic stimulation

Abstract
Objectives. — Peripheral neuropathic pain (pNeP) is prevalent, and current treatments, including drugs and motor cortex repetitive transcranial magnetic stimulation (rTMS) leave a substantial proportion of patients with suboptimal pain relief.
Methods. — We explored the intensity and short-term duration of the analgesic effects produced in pNeP patients by 5 days of neuronavigated deep rTMS targeting the posterior superior insula (PSI) with a double-cone coil in a sham-controlled randomized cross-over trial.
Results. — Thirty-one pNeP patients received induction series of five active or sham consecutive sessions of daily deep-rTMS to the PSI in a randomized sequence, with a washout period of at least 21 days between series. The primary outcome [number of responders (>50% pain intensity reduction from baseline in a numerical rating scale ranging from 0 to 10)] was significantly higher

* Corresponding author at: Divisão de Clínica Neurocirúrgica do Hospital das Clínicas da FMUSP, Instituto Central, Av. Dr. Enéas de Carvalho Aguiar, 255, 5° Andar, Sala 5084, Cerqueira César, 05403-900, São Paulo, Brazil.
E-mail address: ciampi@usp.br (D. Ciampi de Andrade).

https://doi.org/10.1016/j.neucli.2021.06.003

APPENDIX M — Published article “Dry needling has lasting analgesic effect in shoulder pain: a double-blind, sham-controlled trial.”

General Section
Research Paper

OPEN

PAIN REPORTS®

Dry needling has lasting analgesic effect in shoulder pain: a double-blind, sham-controlled trial

Marcus Yu Bin Pai[a,b], Juliana Takiguti Toma[a], Helena Hideko Seguchi Kaziyama[a,b], Clarice Listik[a], Ricardo Galhardoni[a], Lin Tchia Yeng[a,b,c], Manoel Jacobsen Teixeira[a,c], Daniel Ciampi de Andrade[a,c,*]

Abstract

Introduction: Myofascial pain syndrome (MPS) affects most patients with chronic shoulder pain. Dry needling (DN) is a common treatment for MPS, but its temporal pattern and sensory effects remain unknown.

Objectives: We evaluated in a randomized, sham-controlled study the pattern of analgesic efficacy and local sensory changes of a single session of DN for MPS in patients with chronic shoulder pain.

Methods: Patients with chronic shoulder pain were randomized into active (n = 20) or sham (n = 21) groups. A single DN was performed by a researcher blinded to group assignment and pain outcomes. Pain intensity was assessed by the numeric rating score, and sensory thresholds were evaluated with a quantitative sensory testing protocol, including the area of tactile sensory abnormalities 7 days before needling, right before, and 7 days after the intervention.

Results: Dry needling led to significant larger pain intensity reduction (from 6.30 ± 2.05 to 2.40 ± 2.45 in the active group; $P = 0.02$, effect size = −1.3 (95% CI [−2.0 to −0.68]); (number necessary to treat = 2.1). Pain reduction scores were significantly different on the second day after needling and persisted so until the seventh day and were accompanied by improvement in other dimensions of pain and a decrease in the area of mechanical hyperalgesia in the active DN group alone ($P < 0.05$).

Conclusion: Active trigger points DN provided analgesic effects compared with sham and decreased the area of local mechanical hyperalgesia. These findings have practical clinical implications and may provide mechanistic insights behind MPS.

Keywords: Myofascial pain, Chronic pain, Dry needling, Trigger points, Shoulder pain, Quantitative sensory testing

1. Introduction

Musculoskeletal pain disorders rank as the 10th leading cause of years lived with disability worldwide.[27] Shoulder pain is responsible for up to 20% of musculoskeletal complaints,[39,52] leading to inability to work, loss of productivity, and a considerable burden for the patient and society.[42] Shoulder pain is a common complaint in all ages, and it is one of the major reasons why patients consult with primary health care providers.[23,42] The lifetime prevalence of shoulder disorders may affect up to 70% of the population.[8]

Myofascial pain syndrome (MPS) is characterized by local and referred pain because of the occurrence of tenderness in a taut, palpable band of muscle fibers, where painful hyperalgesic myofascial trigger points (MTrP) are identified by manual palpation.[32] Myofascial trigger points occur due to dysfunctional endplate potential and excessive acetylcholine release in the neuromuscular junction that prevents muscle fibers from fully relaxing. It usually arises from muscle overload secondary to inadequate postures or overuse from repetitive activities or as part of referred pain from deeper injured structures, resulting in increased local tenderness and pain.[9,21,30]

Myofascial pain syndrome is highly prevalent and is considered one of the most common mechanisms behind shoulder disorders, affecting up to 95% of patients.[50] Myofascial pain syndrome is frequently found in nociceptive shoulder pain and is believed to be the main cause of pain or coexist and contribute to shoulder pain occurring due to other etiologies, such as subacromial impingement syndrome bursitis, and rotator cuff syndrome.[6] Myofascial pain syndrome is associated with disability and dysfunction because of decreased range of motion of the girdle joints.[6]

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

[a] LIM-62, Pain Center, Department of Neurology, University of São Paulo, São Paulo, SP, Brazil, [b] Division of Physical Medicine and Rehabilitation, Instituto de Ortopedia e Traumatologia, University of São Paulo, São Paulo, SP, Brazil, [c] Pain Center, Instituto do Câncer Octavio Frias de Oliveira, University of São Paulo, São Paulo, SP, Brazil

**Corresponding author. Address: Divisão de Clínica Neurocirúrgica do Hospital das Clínicas da FMUSP, Instituto Central, Av. Dr. Enéas de Carvalho Aguiar, 255, 5° andar, sala 5084, Cerqueira César 05403-900, São Paulo, Brazil. Tel.: 155 11 26 61 71 52. E-mail address: ciampi@usp.br (D. Ciampi de Andrade).*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painrpts.com).

PR9 6 (2021) e939

http://dx.doi.org/10.1097/PR9.0000000000000939

APPENDIX N — Published article “Dissecting neuropathic from poststroke pain: the white matter within”

Research Paper

PAIN®

Dissecting neuropathic from poststroke pain: the white matter within

Marcelo Delboni Lemos[a], Isabelle Faillenot[b], Leandro Tavares Lucato[a], Manoel Jacobsen Teixeira[c], Luciana Mendonça Barbosa[c], Eduardo Joaquim Lopes Alho[c], Adriana Bastos Conforto[d], Antonia Lilian de Lima Rodrigues[c], Ricardo Galhardoni[c], Valquíria Aparecida da Silva[c], Clarice Listik[c], Jefferson Rosi[c], Roland Peyron[b], Luis Garcia-Larrea[b], Daniel Ciampi de Andrade[c,e,*]

Abstract

Poststroke pain (PSP) is a heterogeneous term encompassing both central neuropathic (ie, central poststroke pain [CPSP]) and nonneuropathic poststroke pain (CNNP) syndromes. Central poststroke pain is classically related to damage in the lateral brainstem, posterior thalamus, and parietoinsular areas, whereas the role of white matter connecting these structures is frequently ignored. In addition, the relationship between stroke topography and CNNP is not completely understood. In this study, we address these issues comparing stroke location in a CPSP group of 35 patients with 2 control groups: 27 patients with CNNP and 27 patients with stroke without pain. Brain MRI images were analyzed by 2 complementary approaches: an exploratory analysis using voxel-wise lesion symptom mapping, to detect significant voxels damaged in CPSP across the whole brain, and a hypothesis-driven, region of interest–based analysis, to replicate previously reported sites involved in CPSP. Odds ratio maps were also calculated to demonstrate the risk for CPSP in each damaged voxel. Our exploratory analysis showed that, besides known thalamic and parietoinsular areas, significant voxels carrying a high risk for CPSP were located in the white matter encompassing thalamoinsular connections (one-tailed threshold $Z > 3.96$, corrected P value <0.05, odds ratio $= 39.7$). These results show that the interruption of thalamocortical white matter connections is an important component of CPSP, which is in contrast with findings from nonneuropathic PSP and from strokes without pain. These data can aid in the selection of patients at risk to develop CPSP who could be candidates to pre-emptive or therapeutic interventions.

Keywords: Poststroke pain, Neuropathic pain, Stroke, Chronic pain, White matter

1. Introduction

Stroke is a leading cause of morbidity and mortality worldwide.[38] It is estimated that around 7% to 10% of stroke survivors develop central poststroke pain (CPSP),[43] one of the most refractory pain syndromes, with mechanisms still poorly understood. The search for brain areas related to CPSP has been fueled not only by the need to understand its pathogenesis but also by a pragmatic view centered on offering prophylactic interventions for those at risk.[58]

The thalamus has been implicated in CPSP since 1906,[24] being widely acknowledged to be one of the main areas involved in the syndrome. Around the 1930s, new observations[21,31,71] suggested that extrathalamic brain lesions could also lead to CPSP. The term "pseudothalamic pain syndrome" was then coined, referring to brain areas that, when lesioned, could induce signs and symptoms similar to the ones assigned to the thalamus. Although such areas were initially considered to be restricted to the parietal cortex,[63,64] other brain sites were soon implicated, such as the posterior insula[82] and its adjoining medial operculum region (PIMO).[7] Currently, CPSP is believed to be related to spinothalamic system damage,[37] although this alone seems insufficient for its emergence[27] because clinical factors such as stroke severity and premorbid depressive symptoms may also play a role.[70]

Despite the growing body of neuroimaging data supporting the role of these areas in CPSP,[59,86,89] there are still caveats in the literature that deserve attention. A meta-analysis of CPSP neuroimaging articles revealed that 4 out of 7 studies did not have a control group.[85] When present, control groups consisted of patients with stroke without pain, whereas patients with nonneuropathic poststroke pain (CNNP) were never included. Poststroke pain is a broad, heterogeneous term that includes not only central neuropathic pain (ie, CPSP) but also more frequent pain types such as painful spasticity, tension-type headache, and shoulder pain, among others.[57] Moreover, previous reports tend to focus on structures already described as related to CPSP,

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

[a] Department of Radiology, LIM-44, University of São Paulo, São Paulo, Brazil, [b] NeuroPain Team, Lyon Neuroscience Research Center (CRNL), Inserm U1029, CNRS UMR5292, UCBL1, UJM, F-6900, Lyon, France, [c] Pain Center, Department of Neurology, LIM-62, University of São Paulo, São Paulo, Brazil, [d] Department of Neurology, LIM-62, University of São Paulo, São Paulo, Brazil, [e] Pain Center, LIM-62, Instituto do Câncer do Estado de São Paulo—Octavio Frias de Oliveira, University of São Paulo, São Paulo, Brazil

**Corresponding author. Address: Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, Instituto do Câncer do Estado de São Paulo, Av. Dr. Enéas de Carvalho Aguiar, 255, 5° andar, sala 5084, 05403-900, São Paulo, Brazil. Tel.: 55 11 26 61 71 52. E-mail address: ciampi@usp.br (D. Ciampi de Andrade).*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

PAIN 163 (2022) 765–778

http://dx.doi.org/10.1097/j.pain.0000000000002427

APPENDIX O — Published article “Sorting pain out of salience: assessment of pain facial expressions in the human fetus.”

Pediatric
Research Paper

OPEN

PAIN REPORTS®

Sorting pain out of salience: assessment of pain facial expressions in the human fetus

Lisandra S. Bernardes[a,b,c], Mariana A. Carvalho[a], Simone B. Harnik[d], Manoel J. Teixeira[e], Juliana Ottolia[a], Daniella Castro[f], Adriano Velloso[f], Rossana Francisco[a], Grupo de Estudo da Dor Fetal (Fetal Pain Study Group), Clarice Listik[e], Ricardo Galhardoni[e], Valquiria Aparecida da Silva[e], Larissa I. Moreira[e], Antonio G. de Amorim Filho[a], Ana M. Fernandes[a,e], Daniel Ciampi de Andrade[e,g,*]

Abstract

Introduction: The question of whether the human fetus experiences pain has received substantial attention in recent times. With the advent of high-definition 4-dimensional ultrasound (4D-US), it is possible to record fetal body and facial expressions.

Objective: To determine whether human fetuses demonstrate discriminative acute behavioral responses to nociceptive input.

Methods: This cross-sectional study included 5 fetuses with diaphragmatic hernia with indication of intrauterine surgery (fetoscopic endoluminal tracheal occlusion) and 8 healthy fetuses, who were scanned with 4D-US in 1 of 3 conditions: (1) acute pain group: Fetuses undergoing intrauterine surgery were assessed in the preoperative period during the anesthetic injection into the thigh; (2) control group at rest: Facial expressions at rest were recorded during scheduled ultrasound examinations; and (3) control group acoustic startle: Fetal facial expressions were recorded during acoustic stimulus (500–4000 Hz; 60–115 dB).

Results: Raters blinded to the fetuses' groups scored 65 pictures of fetal facial expressions based on the presence of 12 items (facial movements). Analyses of redundancy and usefulness excluded 5 items for being of low discrimination capacity ($P>0.2$). The final version of the pain assessment tool consisted of a total of 7 items: brow lowering/eyes squeezed shut/deepening of the nasolabial furrow/open lips/horizontal mouth stretch/vertical mouth stretch/neck deflection. Odd ratios for a facial expression to be detected in acute pain compared with control conditions ranged from 11 (neck deflection) to 1,400 (horizontal mouth stretch). Using the seven-item final tool, we showed that 5 is the cutoff value discriminating pain from nonpainful startle and rest.

Conclusions: This study inaugurates the possibility to study pain responses during the intrauterine life, which may have implications for the postoperative management of pain after intrauterine surgical interventions

Keywords: Pain, Fetal, Ultrasound

1. Introduction

The question of whether the human fetus experiences pain has received substantial attention in recent times.[2,9] With the advent of high-definition 4-dimensional ultrasound (4D-US) machines, it has become possible, using high-quality films, to record fetal body and facial expressions.[20] A recent report describing 2 important methodological advances has addressed this challenge by introducing[5]: (1) the possibility of applying a scale based on facial expression originally developed for acute behavioral responses to nociceptive input assessment in neonates (ie, after blood draw) to fetuses and of applying it (2) right after (time anchor) an acute pinprick

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

[a] Disciplina de Obstetrícia, Departamento de Obstetrícia e Ginecologia, Faculdade de Medicina da FMUSP, Universidade de São Paulo, São Paulo, Brazil, [b] School of Medicine, Faculdade Israelita de Ciências da Saúde Albert Einstein, São Paulo, Brazil, [c] Hospital e Maternidade SEPACO, São Paulo, Brazil, [d] Instituto de Matemática e Estatística da Universidade de São Paulo, São Paulo, Brazil, [f] Computational Science Department Universidade Federal de Minas Gerais, Minas Gerais, Brazil, [e] Pain Center, LIM-62, Department of Neurology, University of São Paulo, São Paulo, Brazil, [g] Pain Center, Instituto do Câncer do Estado de São Paulo Octavio Frias de Oliveira, University of São Paulo, São Paulo, Brazil

**Corresponding author. Address: Av. Dr. Enéas de Carvalho Aguiar, 255, 5º andar, Sala 5084, Cerqueira César 05403-900, São Paulo, Brazil. Tel./fax: +55-11-2661-7152. E-mail address: ciampi@usp.br (D. Ciampi de Andrade).*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painrpts.com).

PR9 6 (2021) e882

http://dx.doi.org/10.1097/PR9.0000000000000882

APPENDIX P — Published article “Pharmacological treatment of central neuropathic pain: consensus of the Brazilian Academy of Neurology.”

https://doi.org/10.1590/0004-282X20200166

Pharmacological treatment of central neuropathic pain: consensus of the Brazilian Academy of Neurology

Tratamento farmacológico da dor neuropática central: consenso da Academia Brasileira de Neurologia

Rogério Adas Ayres de OLIVEIRA[1,2], Abrahão Fontes BAPTISTA[3], Katia Nunes SÁ[4], Luciana Mendonça BARBOSA[1,2], Osvaldo José Moreira do NASCIMENTO[2,5], Clarice Listik[1], Xavier MOISSET[6], Manoel Jacobsen TEIXEIRA[1,7], Clinicians participants of the panel of experts recommended by the Brazilian Academy of Neurology[8], Daniel Ciampi de ANDRADE[1,2,7]

ABSTRACT

Background: Central neuropathic pain (CNP) is often refractory to available therapeutic strategies and there are few evidence-based treatment options. Many patients with neuropathic pain are not diagnosed or treated properly. Thus, consensus-based recommendations, adapted to the available drugs in the country, are necessary to guide clinical decisions. **Objective:** To develop recommendations for the treatment of CNP in Brazil. **Methods:** Systematic review, meta-analysis, and specialists opinions considering efficacy, adverse events profile, cost, and drug availability in public health. **Results:** Forty-four studies on CNP treatment were found, 20 were included in the qualitative analysis, and 15 in the quantitative analysis. Medications were classified as first-, second-, and third-line treatment based on systematic review, meta-analysis, and expert opinion. As first-line treatment, gabapentin, duloxetine, and tricyclic antidepressants were included. As second-line, venlafaxine, pregabalin for CND secondary to spinal cord injury, lamotrigine for CNP after stroke, and, in association with first-line drugs, weak opioids, in particular tramadol. For refractory patients, strong opioids (methadone and oxycodone), cannabidiol/delta-9-tetrahydrocannabinol, were classified as third-line of treatment, in combination with first or second-line drugs and, for central nervous system (CNS) in multiple sclerosis, dronabinol. **Conclusions:** Studies that address the treatment of CNS are scarce and heterogeneous, and a significant part of the recommendations is based on experts opinions. The CNP approach must be individualized, taking into account the availability of medication, the profile of adverse effects, including addiction risk, and patients' comorbidities.

Keywords: Pain; Pain management; Neuropathic pain; Drug therapy; Consensus.

RESUMO

Introdução: A dor neuropática central (DNC) é frequentemente refratária às estratégias terapêuticas disponíveis e há poucas opções de tratamento baseado em evidência. Muitos pacientes com dor neuropática não são diagnosticados ou tratados adequadamente. Desse modo, recomendações baseadas em consenso, adaptadas à disponibilidade de medicamentos no país, são necessárias para guiar decisões

[1]Universidade de São Paulo, Faculdade de Medicina, Centro de Dor, Departamento de Neurologia, São Paulo SP, Brazil.

[2]Academia Brasileira de Neurologia, Departamento Científico de Dor, São Paulo SP, Brazil.

[3]Universidade Federal do ABC, Center for Mathematics, Computation and Cognition, São Bernardo do Campo SP, Brazil.

[4]Escola Bahiana de Medicina e Saúde Pública, Graduate and Research Department, Salvador BA, Brazil.

[5]Universidade Federal Fluminense, Faculdade de Medicina, Graduate and Research Program in Neurology/Neurosciences, Niterói RJ, Brazil.

[6]Université Clemont Auvergne, Chu de Clermont-Ferrand, INSERM, NEURO-DOL, F-63000 Clermont-Ferrand, France.

[7]Universidade de São Paulo, Departamento de Neurologia, Centro de Dor, LIM 62, São Paulo SP, Brazil.

[8]Academia Brasileira de Neurologia, Departamento Científico de Dor, São Paulo SP, Brasil. (Abouch Krymchantowski, Alberto Rolim Muro Martinez, Alcione Mendes de Sousa, Alyne Mendonça Marques Ton, Silva Tenorio Luna Sarmento, André Palma da Cunha Matta, Antonio Rodrigues Coimbra Neto, Bruno Bertoli Esmanhotto, Camila Castelo Branco Pupe, Clarice Listik, Eduardo Boiteux Uchôa Cavalcanti, Eliana Meire Melhado, Eustáquio Claret dos Santos, Fabricio Diniz de Lima, Fabíola Dach, Helena Rezende Silva Mendonça, Hilton Mariano, Igor Silvestre Bruscky, Ingrid Faber, Jefferson Borges de Oliveira, Jessyca Luana Alves Koslyk, Jorge Dornellys da Silva Lapa, Jose Fabio Santos Leopoldino, José Geraldo Speciali, Marcelo Rezende Young Blood, Marcelo Silva Cabral, Marcos Moreira, Matheus Gurgel Saraiva, Mauro Eduardo Jurno, Michel Elyas Jung Haziot, Miriam Jaqueline Teixeira, Nestor C Truite Jr, Norma Regina Pereira Fleming, Otto J H Fustes, Patricia Peixoto, Pedro Schestatsky, Renata Gomes Londero, Renato Silva Martins, Sidney Gomes, Welber Sousa Oliveira, Wladimir Bocca V. de Rezende Pinto, Yara Dadalti Fragoso).

Rogério Adas Ayres de OLIVEIRA https://orcid.org/0000-0002-0254-8497; Abrahão Fontes BAPTISTA https://orcid.org/0000-0001-7870-3820; Katia Nunes SÁ https://orcid.org/0000-0002-0255-4379; Luciana Mendonça BARBOSA https://orcid.org/0000-0002-5239-5935; Osvaldo José Moreira do NASCIMENTO https://orcid.org/0000-0003-3516-485X; Clarice LISTIK https://orcid.org/0000-0002-7660-3970; Xavier MOISSET https://orcid.org/0000-0002-8799-0750; Manoel Jacobsen TEIXEIRA https://orcid.org/0000-0002-7974-6045; Clinicians participants of the panel of experts recommended by the Brazilian Academy of Neurology; Daniel Ciampi de ANDRADE https://orcid.org/0000-0003-3411-632X

Correspondence: Daniel Ciampi de Andrade; E-mail: ciampi@usp.br

Conflict of Interest and financial support: KNS (third author) received financial aid from Zodiac Produtos Farmacêuticos to develop this guideline. DCA and AFB received productivity in research scholarships from the National Council for Scientific and Technological Development. All authors declare no other conflicts of interest to develop the study.

Author's contribution: R. A. A. de Oliveira - Methodology, Writing – original draft; A. F. Baptista - Formal Analysis, Writing – original draft; K. N. Sá - Data curation, Formal Analysis; L. M. Barbosa - Funding acquisition, Project administration; O. J. M. do Nascimento – Methodology, Data curation, Visualization; C. Listik - Writing – review & editing; X. Moisset - Formal Analysis, Data curation; M. J. Teixeira - Conceptualization, Methodology; D. C. de Andrade - Conceptualization, Funding acquisition, Project administration, Writing – review & editing; Central Neuropathic Pain Study Group – Methodology, Formal Analysis.

Received on July 4, 2020; Received in its final form on September 6, 2020; Accepted on September 17, 2020.