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RESEARCH ARTICLE

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

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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

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Introduction

Dystonia is a heterogeneous movement disorder of acquired, inherited, or idiopathic causes.[1] Despite different etiological backgrounds, symptoms frequently include motor and nonmotor features.[2] Dystonia is classically defined by its motor manifestations. However, the nonmotor symptoms (NMS) are equally common and may also impact the patient's quality of life (QoL).[3,4] NMSs include pain, sensory abnormalities, mood disorders (depression, anxiety, and obsessive-compulsive disorder), cognitive complaints, sleep disturbances, autonomic symptoms, and fatigue.[3,5] Chronic pain (CP), defined as persistent or recurrent pain lasting longer than 3 months,[6] affects up to 30% of the general population.[7,8] It is especially prevalent in people with dystonia (PwD), up to 90%, depending on the type of dystonia.[5,9-11] Indeed, some reports show that CP may impact QoL more significantly than dystonia's motor severity.[12] Pain significantly contributes to disability, compromising work and daily routine.[10,13,14]

Though prevalent and significantly increasing the burden of the disease, CP has been less studied in dystonia than in other movement disorders.[15] Furthermore, there are currently no specific tools to assess pain in PwD. Therefore, it is unknown whether differentiating de novo pain starting with dystonia from already-existing CPs has clinical relevance. The same is true for the differentiation of patients with previous CP that is aggravated by dystonia from those instances where no change in pain occurs as the disease surges. Additionally, the absence of a specific classification system for CP in dystonia without specific or validated tools to quantify dystonia-related pain intensity, frequency, and functional impairment was identified by our group as an unmet need that could potentially benefit patients. It is highly likely that the lack of specific assessment methods negatively impacts data generation on pain management in dystonia. This gap in knowledge led us to design a multicenter study to develop and test a patient-relevant classification framework for CP in PwD and a scoring system assessing pain intensity, frequency, and functional impact.

Patients and Methods

Design

This was a cross-sectional, multicenter study to develop a CP classification system in dystonia with a complete validation study including a test–retest reliability procedure.

Patients and Consent

Consecutive PwD, with or without CP, were recruited for this study. Informed consent was obtained from all subjects. The coordinating center institutional ethics review board (31832920.2.1001.0068) approved the study protocol.

Patients were included from July 2020 to July 2022. Eight centers were invited to participate, and after online meetings, five were selected. Two 90-minute online training sessions were conducted to determine homogeneity in patient assessment and data collection (through the Research Electronic Data Capture [Redcap] data management platform).[16] Adult patients with a diagnosis of inherited or idiopathic dystonia of any distribution with or without CP were included, according to international guidelines.[1] Patients were excluded if they were cognitively impaired, were unable to communicate (anarthria), or did not consent to participate.

Development of the Dystonia-Pain Classification System

The Dystonia-Pain Classification System (Dystonia-PCS) is a rater-based scale (Fig. 1) inspired by the Parkinson's Disease-Pain Classification System.[15] This classification system was designed according to recommended and established procedures[17] for scale development. Due to the absence of previous CP scales in dystonia, we analyzed the existing classifications of CP in other movement disorders.[15,18-21] Item generation was based on the advice and experience of both movement disorders and pain specialists. Meetings with both specialists were the basis for the questionnaire development, reducing the item pool by rejecting poor or redundant items.

The main aims of Dystonia-PCS were to (1) determine whether pain can be related to dystonia (directly related or aggravated by it) or unrelated to dystonia and (2) to develop a severity score for each type of pain in which the pain's intensity, frequency, and impact on daily living are quantified. The scale aimed to be practical and to quantify the experience of pain in PwD. 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 (Fig. 1). The scores range from 0 to 90 for each pain type. Dystonia-PCS can be applied to any CP the patient presents. When a secondary CP was determined to be spatially or qualitatively different
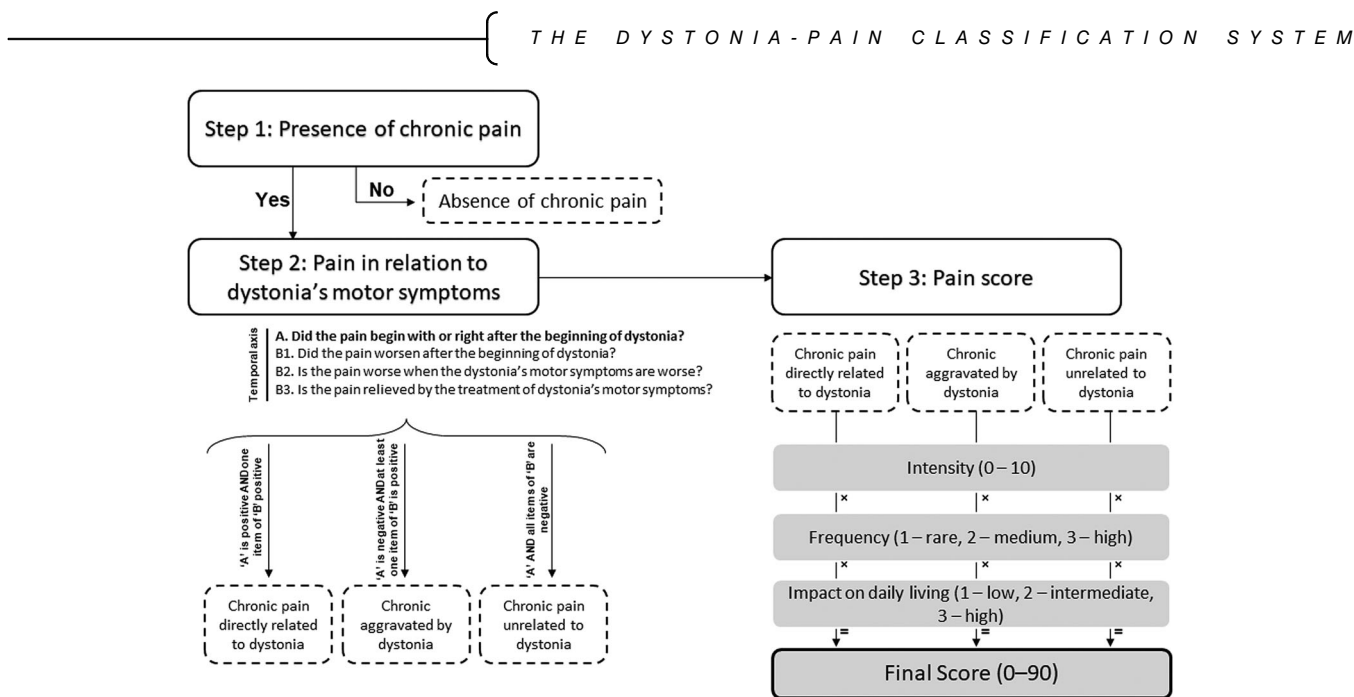
FIG. 1. The Dystonia-Pain Classification System (Dystonia-PCS). Step 1 (n = 123 patients) is to determine whether the pain is chronic. Chronic pain is defined as persistent or recurrent pain lasting longer than 3 months. Step 2 (n = 81 patients) establishes the relationship between pain and dystonia. One can classify the pain by answering four questions (A, B1, B2, and B3). Chronic pain is classified as directly related to dystonia, with question A being affirmative and at least one item of B being affirmative. If question A is negative and at least one item of B is affirmative, then the pain is classified as aggravated by dystonia. If A and all items of B are negative, the pain is classified as unrelated to dystonia. If the pain could not be classified as such, it was deemed "undetermined pain." The final step (step 3, n = 81 patients) is performed by calculating a score in which intensity, frequency, and impact on daily living are multiplied, resulting in a final score ranging from 0 to 90.

from the main pain, the Dystonia-PCS was applied to both, which were classified and scored.

The first step in the Dystonia-PCS is to determine whether the patient has CP. The second step 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 as such, it is called undetermined and is analyzed descriptively. The final step (step 3) calculates a severity score in which intensity, frequency, and impact on daily living are multiplied (Fig. 1). Therefore, the Dystonia-PCS provides in the first two steps a classification framework for CP definition and the relationship with motor symptoms of diseases of the nervous system, respectively. This is in line with the International Classification of Diseases-11 (ICD-11),[22] where CP aggravated or initiated by associated neurological disorders is classified as secondary pain. The third step provides a severity scoring system to assess the present pain burden.

Raters assessed patients' pain using the classification tool in a standardized way. According to regulatory agencies' recommendations on the development of questionnaires and scales,[23,24] the classification system draft was first introduced to a random sample of 8 patients to establish face validity, capture patients' opinions, and estimate assessment time.[11] Then,

patients were asked to rate (on a scale of 1–3: 1 = essential, 2 = useful but not essential, and 3 = unessential) each of the items generated by the steering committee. Items with a content validity ratio of 0.62 were excluded. They were asked if they believed that the items would be able to capture the pain challenges experienced by PwD.

The final scale received input at national and international movement disorders and pain conferences, leading to the Dystonia-PCS consolidation to validate its psychometric properties.[17]

Patient Assessment

PwD were clinically examined and classified[1] by specialists in movement disorders. At baseline, dystonia and clinical history was gathered. Then, motor and nonmotor scales were applied, including mood, QoL, and pain scales. The motor assessment included the motor (0–120) and disability subscores (0–29) of the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS).[25] For mood and QoL assessments, the Hospital Anxiety and Depression Scale (HADS)[26,27] and the European QoL-5 Dimensions-3 Level Version, known as EuroQol-5D-3L (EQ),[28] were applied, respectively.

Pain was assessed using the Brief Pain Inventory (BPI) short-form[29,30] and the Douleur Neuropathique-4 (DN4) questionnaire.[31,32]

Patients were asked whether they had pain (hereafter described as main CP) most of the days lasting more than 3 months and to indicate on an electronic mannequin the space location of their main CP. In addition, because it has been shown that CP patients, in general, frequently present with more than one pain syndrome,[15,33] patients were allowed to indicate whether they had a second CP that was spatially different from the main pain and less bothersome (henceforth named secondary CP). Thus, the main and secondary CP were evaluated by the Dystonia-PCS. Eight researchers were responsible for patient assessment and participated in the intra- and inter-rater reliability assessments. A sample of CP patients was reassessed 6 months to 2 years after the initial interview to assess long-term sensitivity to change of the Dystonia-PCS. In these later instances, assessments were made by a structured conference with information on the presence of CP, QoL (EQ's Visual Analog Scale [VAS]), pain intensity (BPI's pain intensity items 3–6), and the Dystonia-PCS.

Sample Size and Data Analyses

See Supplementary Material in Data S1.

Results

Overall Clinical Features

See Supplementary Material in Data S1.

Chronic Pain

CP was present in 65.8% of patients (n = 81). Patients with and without CP had similar clinical, demographic, and dystonic characteristics (ie, dystonia's duration, distribution), only diverging in treatment with trihexyphenidyl and proportion of sex (Supplementary Table 1 in Data S1). The distribution of dystonia did not affect the Dystonia-PCS score (P = 0.371).

Groups did not differ regarding the motor and QoL scores (Supplementary Table 2 in Data S1). However, depression and anxiety were significantly worse in patients with CP, and semantic verbal fluency was better in these patients. CP had an intensity of 4.84 ± 2.50 (0–9.25) and pain interference of 4.26 ± 3.22 (0–10) on BPI. Twenty-four patients (30.37%) had neuropathic pain, according to DN4. Thirty-eight patients with CP (46.91%) revealed more than one site of pain (25 had two different CPs, 7 had three CPs, 3 had four CPs, and 3 had more than four different pains).

For the main CP (Table 1), 67 (82.7%) were directly related to dystonia, 7 (8.8%) were aggravated by dystonia, 6 (7.5%) were nonrelated to dystonia, and 1 was undetermined (1.2%). The main CP was most frequently localized in the cervical region (n = 52, 64.2%), followed by cephalalgia and low-back pain (n = 5), shoulder pain, and knee pain (n = 4), and other types of pain (upper limb, n = 3; lower limb, n = 2; interscapular pain, n = 1; dorsal pain, n = 1; maxilla pain, n = 1; eye pain, n = 1; foot pain, n = 1; and hip pain, n = 1, Supplementary Figure 1 in Data S1). 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 (Supplementary Table 3 in Data S1). Thirty-eight patients had a secondary CP (Table 1; Supplementary Material in Data S1).

We further analyzed whether oral pharmacological treatment, botulinum toxin, or deep brain stimulation (DBS) influenced pain and Dystonia-PCS scores (Supplementary Tables 4–6 in Data S1). There were no differences between treated and nontreated groups. We compared pain and Dystonia-PCS scores of patients with shorter (p25th) and longer (p75th) dystonia duration (Supplementary Table 7 in Data S1). There were also no differences.

We further compared whether patients with cervical dystonia (CD), the largest proportion of our patients, had different pain and Dystonia-PCS scores compared to non-CD patients (Supplementary Table 8 in Data S1). They had similar results, though this needs to be interpreted with caution because patients with generalized, multifocal, and segmental dystonia may have a CD component.

Acceptability

All patients underwent the first step (n = 123), and those with CP (n = 81) underwent the following steps of the scale. Dystonia-PCS has a floor effect of 0% to 2.9% based on the subtype of pain and a ceiling effect of 10.5% to 16.7% (Table 2). Raters informed that Dystonia-PCS took 8.12 ± 4.43 (4–15) minutes to be applied.

Internal Consistency

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

Test–Retest Reliability

Thirty-seven patients (45.67%) with CP were retested in a short term (Table 3). 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 3).

TABLE 1 *Chronic pain characteristics*

Variables	Main chronic pain*	Secondary chronic pain*
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)	

(Continues)

TABLE 1 *Continued*

Variables	Main chronic pain*	Secondary chronic pain*
DN4	2.43 ± 1.87 (0–7)	
DN4 positive	24 (30.37%)	
Dystonia-PCS		
Related	67 (82.7%)	22 (57.9%)
Aggravated	7 (8.8%)	10 (26.3%)
Unrelated	6 (7.5%)	4 (10.5%)
Dystonia-PCS score		
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)

Note: Data are presented as n (%) or mean ± standard deviation (min–max).
*Main chronic pain (n = 81) and secondary chronic pain (n = 38); Only 1 patient had a main chronic pain classified as undetermined pain, whereas 2 patients had secondary pain classified as such.
Abbreviations: BPI, Brief Pain Inventory; BPIs, BPI severity subscore; BPIi, BPI interference subscore; DN4, Douleur Neuropathique 4; Dystonia-PCS, Dystonia-Pain Classification System.

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 was excluded from the individual analysis, calculated only for the directly related pain (Table 3).

Criterion Validity and Convergent and Divergent Construct Validity

The Dystonia-PCS directly related score is significantly associated with the EQ pain subscore, BPI (severity and interference subscores), and DN4 score. For all CP patients, our scale was significantly associated with the EQ pain subscore, all BPI scores, the DN4 score, the total HADS score, and the anxiety HADS subscore (Table 4). It shows that the pain classification has an association with other pain scales. The Dystonia-PCS score did not correlate with the BFMDRS.

Known Group and Internal Validity

A multinominal logistic regression analysis was performed to assess factors associated with the Dystonia-PCS (Supplementary Table 9 in Data S1). Patients with CP related to dystonia directly correlated to DN4 (coefficient 18.752 ± 1.760, $P < 0.001$) and EQ pain

TABLE 2 *Acceptability*

Dystonia-PCS[a,b]	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	$P = 0.025$	$P = 0.105$	$P = 0.189$

[a]Internal consistency of the scale is ICC = 0.925, $P = 0.0001$.
[b]Undetermined scale had only 1 patient, which made the analysis impossible.

subscores (coefficient 2.830 ± 1.210, $P = 0.023$). These patients' scores did not correlate with motor severity or disability.

Comparison between the Types of Pain

We compared the different pain subtypes, and only the EQ-VAS subscore was different between them, with the patients with directly related pain showing lower scores than those with unrelated pain or aggravated pain, respectively (61.45 ± 26.34 vs. 81.67 ± 17.22 vs. 84.29 ± 11.34, $P = 0.021$). Pain location was not different between the subtypes.

Long-Term Evaluation of Chronic Pain

Twenty PwD were evaluated 1.58 ± 0.59 (0.67–2.12) years after their initial evaluation. Sixteen had CP in the first evaluation, whereas 12 had CP on long-term

evaluation. Three patients did not have CP and maintained that status, whereas 1 patient who did not have CP previously had a low-back pain after the first assessment.

The Dystonia-PCS, EQ-VAS, and items 3 to 6 of the BPI were applied in this long-term reevaluation (Supplementary Tables 10 and 11 in Data S1). There was a positive correlation between the BPI's intensity subitem deltas (worst pain 0.649, $P = 0.002$; least pain 0.454, $P = 0.044$; and average pain 0.562, $P = 0.010$) and the classification delta.

Sensitivity Analyses

To assess the psychometric properties of the Dystonia-PCS in patients without CD, we performed all the analyses for this group (Supplementary Table 12A-- D in Data S1). They still had the cervical location as

TABLE 3 *Dystonia-PCS scores assessed on two occasions (n = 37) and intra- and inter-rater reliability*

Dystonia-PCS	Visit 1	Visit 2	Delta	*P*
Dystonia-PCS				
Related	32 (86.5%)	31 (83.8%)	–	0.415
Dystonia–PCS score				
Related	46.44 ± 23.15 (2–90)	47.48 ± 26.10 (6–90)	-0.45 ± 9.55 (−30 to −36)	0.877
Dystonia-PCS	**Intra-rater[1]**	***P***	**Inter-rater[1]**	***P***
Dystonia–PCS	0.792★★★	<0.001	0.207	0.054
Related	0.773★★★	<0.001	0.941★★	0.003
Dystonia–PCS score	0.941★★★	<0.001	0.867★★★	<0.001
Related	0.944★★★	<0.001	0.868★★	0.005

[1]Number of pain assessments (data from the main and secondary chronic pain) were n = 45 for intra-rater reliability and n = 13 for inter-rater reliability. Number of patients: intra–rater reliability (n = 28) and inter-rater reliability (n = 9).
Note: Data are presented as n (%) or mean ± standard deviation (min–max).
★$P < 0.05$.
★★$P < 0.01$.
★★★$P < 0.001$.
Abbreviation: Dystonia-PCS, Dystonia–Pain Classification System.

TABLE 4 *Correlations between Dystonia-PCS scores and other variables at visit 1*

Scales	Dystonia-PCS score[1]	P	Dystonia-PCS-related subscore[1]	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

[1]Dystonia-PCS score (n = 81) and Dystonia-PCS-related score (n = 60).
★P < 0.05.
★★P < 0.01.
★★★P < 0.001.
Abbreviations: Dystonia-PCS, Dystonia–Pain Classification System; 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.

their main pain location. Good intra-rater reliability, correlation with other pain scales, acceptability, and internal consistency remained. However, the smaller size of this sample negatively impacted the inter-rater reliability assessment.

Discussion

The Dystonia-PCS is an original pain classification and scoring tool for dystonia. It was based on the three main steps of pain assessment in patients with neurological diseases: assessment of chronicity (step 1), analysis if it is secondary to the disorder (step 2), and assessment of its burden (step 3).[15,19] It showed good patient acceptance, psychometric qualities in patients with different disease duration, background motor treatment, and dystonia's location. The Dystonia-PCS had adequate internal consistency and excellent intra- and inter-rater reliability. The system had competent convergent and divergent validity, which was confirmed by high correlations with commonly used pain questionnaires. Its psychometric properties indicate that it is a valuable tool for evaluating CP in dystonia.

Pain in dystonia was reported in both DBS[4] and botulinum toxin studies,[11,34] generally using the pain sub-items of QoL scales[35] or the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)[34] or even unidimensional scales like VAS for pain intensity.[3,11] The Dystonia-PCS will aid in further

characterizing whether pain in PwD is chronic, actually related to the disease, and provide a severity score that considers functional impairment, beyond pain intensity, similar to current multidimensional approaches to classify pain in Parkinson's disease (PD).[15,19,36]

Most studies reporting on pain in PwD were centered exclusively on focal and segmental dystonia, more commonly CD.[4] In this type of dystonia, up to 90% of patients have pain.[11] The TWSTRS is a scale specific for CD and has a pain subitem,[37] in which the rater scores the pain's severity (for the worst, best, and usual pain), the duration of pain, and its disability. It is an important assessment tool, but it currently does not allow to discriminate whether the pain is chronic as it asks to rate the severity of neck pain due to spasmodic torticollis during the previous week. The Dystonia NMS Questionnaire (DNMSQuest) is validated for CD and addresses the presence of unpleasant sensations such as numbness, tingling, or pins and needles in the body area at or near the dystonic area.[38] We found that the Dystonia-PCS could also be applied to patients with other dystonia types besides CD while maintaining its main clinimetric qualities. However, patients with segmental, multifocal, and generalized dystonia may also have CD as part of their dystonia. This may have influenced our results (see legend of Supplementary Table 12A–D in Data S1).

Though some studies describe PwD's pain, it is usually not specified if the patient has CP, which has important prognostic and management implications. The Dystonia-PCS fills this gap by specifically allowing for the diagnosis of CP while opening the possibility of addressing its cause, such as low-back pain,[39] headache,[40] or neuropathic pain. 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.[22]

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. Although the mixed pain concept has been reported in the general pain field and in pain in PD, it has not yet been explored in dystonia.[33,41] 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.[12] Additionally, efficacious treatments to control dystonic movements may not wholly mitigate pain in PwD, which persists despite improvement in motor symptoms.[35,42] The main driving mechanism of dystonia is believed to be the reduction in cortical inhibition,

impaired synaptic plasticity, and altered gain in somatosensory processing.[43-49] 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.

Dystonia is a circuit disorder involving the basal ganglia-thalamocortical and the cerebellum-thalamocortical circuits.[10,50,51] The basal ganglia are responsible for the integration of motor, emotional, autonomic, and cognitive processes, probably including mood and pain.[52] Indeed, PwD have both peripheral[53-56] and central[10,57,58] sensory abnormalities, with defective processing of nociceptive stimuli integration.[59] Despite these common mechanisms behind pain and motor symptoms in dystonia, there is no linear relationship between motor symptoms and NMS in terms of response to treatment. We have evaluated PwD who have an established dystonia diagnosis and were under optimized treatment for their motor symptoms. It is known that dystonia's treatment may improve pain,[4,10,60,61] though it may persist even after DBS[42] or botulinum toxin injections.[35] Although our study was not designed to evaluate the frequency or prevalence of CP in PwD, it suggests that CP is present despite optimized motor control.

One common challenge when assessing pain related to a specific disease is that CP has a baseline prevalence of about 20% of the general population globally.[62] Although determining causality is a philosophical and scientific challenge, the 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.[22] This is how pain related to multiple sclerosis,[63] PD,[15] and stroke[64] is 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/nonpain symptoms of the disease. If, on the one hand, this may be prone to recall bias, especially in long-standing 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. Although recall bias is very likely to exist, its magnitude is unknown. And based on our data, patients with longer and shorter disease durations presented similar scores in the assessments. This also supports the long-acknowledged lack of correlation between motor symptom severity and pain intensity in movement disorders such as PD and dystonia.[4,5,42,56,65] One important aspect is that the

aforementioned potential bias refers to pain classification in step 2. The determination of pain chronicity (step 1) was based on a classic 3-month cutoff, which has been extensively validated and is recommended to classify pain as chronic.[66] In step 3, pain severity assessment was based on the present pain, as is commonly used for most pain assessment tools. Besides the aforementioned potential recall bias 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 (eg, 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 ensured and allowed the classification system to perform well in psychometric and validation tests. Overall, the 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 (eg, post-surgery [MG30.2], post-stroke [MG 30.50], or PD-related pains [MG30.32], including chronic secondary musculoskeletal pain associated with PD).[22] According to the ICD-11 approach, pain directly related to dystonia would be secondary.[22] And for that, the crucial point is its temporal relationship with the disease (ie, dystonia) start. We followed this same approach here. Thus, based on the ICD-11 approach and societal recommendations,[22] dystonia-related pain is a secondary pain syndrome classified based on its temporal and symptomatic relationship to the disease.[66-68] Therefore, we chose to divide the pain based on the time that the motor symptoms appeared because the patient may usually differentiate if the pain began before, during, or after the motor symptom 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.[36] 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 compared whether patients with short- versus long-standing dystonia showed similar scores in pain questionnaires and in the Dystonia-PCS (Supplementary Table 7 in Data S1).

A general lack of correlation between pain intensity and dystonia severity[4,5,12,69] has been repetitively reported, something also true for other diseases like PD.[36] This may suggest that the neuronal processes responsible for pain initiation and maintenance are probably different from those responsible for motor symptom 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 related to the disease, followed by the determination of current intensity and impact of pain. Here too, pain intensity did not correlate with severity of motor symptoms. This further supports the view that motor symptoms and NMS such as pain are likely to not only depend on different mechanisms but also respond differently to treatment and have different prognoses.[42,56]

The Dystonia-PCS created a scaffold for further classification of pain attempts, such as efforts to provide mechanism-based classifications of pain in PwD such as the use of neuropathic or nociceptive mechanistic descriptors.[15] Although this additional step is commonly attempted in clinical practice when caring for PwD and pain, sufficient information on the mechanisms of subtypes of CP in dystonia is not currently available to include them in the Dystonia-PCS. This leads the steering committee responsible for the development of the Dystonia-PCS to refrain from having this step and leaving a gap open for the framework to gain a fourth step in the future should more mechanistic information on pain in dystonia become available.

Another point of discussion is the inclusion of any type of dystonia. Although it is reasonable that a specific CP tool for each type of dystonia could be useful and potentially more specific, we chose to include the largest number of patients possible in this first attempt. The main reason is that it is unclear what the best way to segregate patients for a specific pain assessment tool is. For focal dystonia alone, one faces CD, blepharospasm, Meige syndrome, laryngeal dystonia, task-specific dystonia, focal hand dystonia, and foot dystonia. Therefore, we aimed for a general system for CP classification that does not consider dystonia location in its steps. This strategy leaves open enough room for further efforts to add supplementary-specific dystonia-type-relevant add-ons to the classification system, which can be specifically validated in dystonia types/locations. Our sensitivity analyses supported this approach showing that most of the properties of the Dystonia-PCS remain when assessing non-CD patients.

This study has some important limitations. As the patients were seen in specialized centers, our sample has an overrepresentation of primary CD. This may have further influenced our results toward an overrepresentation 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 underrepresented 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 patients themselves.[70] Although we had rounds of patient meetings and inputs in our classification system, they were limited to a small number of patients and from a limited number of centers. Additionally, the role of patients was observed 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.

Conclusion

We have reported on the development and validation of the Dystonia-PCS, which aims to classify CP in dystonia. It is a quick-application questionnaire that could improve PwD's treatment, QoL, and symptomatic control. Crucial to its application, the Dystonia-PCS shows high reliability and correlates significantly to established pain scales. ●

Data Availability Statement

All data used in this study are available from the corresponding authors upon reasonable request.

Appendix

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.