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RESEARCH ARTICLE

# External Factors Modulating Pain and Pain-Related Functional Impairment in Cervical Dystonia

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**Abstract:** Background: Little is known about factors modulating pain and pain-related functional impairment in isolated cervical dystonia (CD).

Objective: The aim was to assess the prevalence and interrelationship between pain-modulating factors and pain-related determinants of functional impairment and quality of life in CD.

Methods: We analyzed pain-aggravating and pain-relieving external factors, the degree of pain-related functional impact on routine activities, and the relationship between these and pain severity, using cross-sectional data collected using the Pain in Dystonia Scale (PIDS) from 85 participants with CD. Pairwise correlation analyses and age- and sex-adjusted linear regression models estimated the relationship between pain-modulating factors and pain severity, and the impact of pain severity, dystonia severity, and psychiatric symptoms on pain-related functional impairment and disease-specific quality of life (measured using the Craniocervical Dystonia Questionnaire-24).

Results: Stress and prolonged fixed position were the most frequent and impacting pain triggers, with women reporting larger impact. The average impact of pain-relieving factors was lower than that of pain triggers. Physical exercise and social gatherings were the most impacted activities by pain in CD. The intensity of external modulating factors was a predictor of pain severity. Severity of pain, CD, and psychiatric symptoms independently predicted pain-related functional impairment, whereas quality of life was predicted by pain severity, pain-related functional impairment, and psychiatric symptom severity, but not dystonia severity.

Conclusion: The PIDS provides insight into external modulation and functional impact of pain in CD. The pattern of external modulation of pain in CD is in line with a multifactorial modulation and complex physiology.

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Pain is a prominent feature of adult-onset isolated dystonia (AOID).[1,2] Isolated cervical dystonia (CD) is the most common focal AOID and the one most frequently associated with pain, including musculoskeletal pain, pain secondary to muscle spasms and abnormal postures, and occasionally neuropathic pain.[3] Pain is reported by 54.6% to 88.9% of CD patients. Alongside anxiety and depression, pain exerts the greatest influence on these patients' quality of life.[2–6] Cervical and shoulder regions are the most frequently painful areas[3]; however, pain in the cranial region, upper extremities, trunk, and spine is not uncommon. The mechanisms underlying the spread of pain beyond the neck in CD include sustained muscle contractions of neck muscles affecting adjacent areas, compensatory postures to alleviate discomfort, placing stress on other body parts, potentially abnormal neural pathways enhancing pain sensitivity or causing pain perception in areas remote from the dystonic site(s), joint stress, and radicular involvement due to compression or irritation.[3] Patients with CD describe their pain as "prickly," "neck-pulling," "radiating," and even "exhausting."[3] Different forms of chronic headache are reported by 10% to 20% of CD patients, involving, in decreasing order of prevalence, the occipital, cervical, temporal, frontal, vertex, and retroorbital regions.[3,7,8] Dystonic movements are also considered common migraine triggers in people with CD.[7] Finally, CD patients may suffer from pain in other body regions manifesting dystonia, for example, ocular dysesthesia and photo-oculodynia in blepharospasm,[9,10] jaw pain in oromandibular dystonia,[11] limb pain in upper-limb dystonia,[3,12] and throat pain sometimes reported in laryngeal dystonia.[13]

In CD, pain severity is positively related to the severity of abnormal postures and movements. Pain correlates with gait performance when patients rely only on their body position awareness and sense of straightness.[14] CD patients reporting pain have a 2.5 to 3 times higher probability of identifying 1 or more alleviating maneuvers to relieve both motor symptoms and pain.[4,15] Pain is one of the main determinants of the mismatch between clinician-based and patient-based ratings of CD severity.[16] A substantial improvement in pain after botulinum neurotoxin injection cycles or globus pallidus internus deep brain stimulation is reported by most patients with CD,[17–19] although over-the-counter painkillers are also commonly used.

Pain in CD is typically conceptualized as secondary to sustained contractions of cervical muscles, as corroborated by the practical notion that "following the pain" during botulinum neurotoxin administration increases treatment success.[20] At the same time, pressure algometry failed to demonstrate a strong relationship between pain and the degree of contraction of dystonic muscles.[21] This, coupled with a mismatch in treatment response between motor manifestations and pain,[22] suggests the presence of both nociplastic and nociceptive contributors to pain in CD. Therefore, a conditioned pain modulation protocol demonstrated defective functioning of the endogenous descending inhibitory pain system in CD patients, regardless of the presence of pain.[23] The experience of pain in CD may also be influenced by factors that are external to dystonia. For example, a catastrophic interpretation of pain appears more closely linked to concurrent depression and anxiety.[24]

Prior to 2023, the clinimetric assessment of pain in CD was limited to the pain subscale of the 2 versions of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS).[25,26] Recently, we developed the Pain in Dystonia Scale (PIDS), the first disease-specific instrument to assess pain across different body regions regardless of the anatomical distribution of dystonia.[27] This characteristic makes it applicable to all patients with AOID, enabling clinicians and researchers to evaluate pain in a dystonic region (thus more tightly linked to sustained muscle contractions) independently of pain in other regions. To date, the PIDS has been validated only in CD[27] and comprises a severity scale, a functional impact measure, and a questionnaire collecting data on pain-modulating factors. The PIDS pain severity score has demonstrated excellent convergent validity with the TWSTRS pain subscale and mild correlation with the Global Dystonia Rating Scale score.[27] Another multidisciplinary group has developed the Dystonia-Pain Classification System, which categorizes and quantifies the impact of chronic pain in dystonia.[28] These novel instruments may improve clinicians' ability to rate pain in dystonia and measure more accurately pain response to existing or novel therapies. In addition, the PIDS is the first instrument to provide a comprehensive, personalized profile of pain in individual patients with dystonia, due to the self-evaluation of external factors that can trigger/worsen or alleviate/relieve pain, although previous studies also applied a visual analogue scale to assess pain in CD.[29,30] Very little is known about these external modulating factors. A better understanding of these factors would inform how certain lifestyle aspects influence pain in dystonia, and how to modify these to improve pain and even suggest mechanisms through which these exert their influence, advancing our understanding of the pathophysiology of pain in dystonia.

To this end, we summarize here the prevalence and interrelationship between external pain-modulating factors measured using the PIDS and the impact of pain severity, external pain modulation, and other clinical characteristics of pain-related functional impairment and quality of life in patients with CD.

# Patients and Methods

This was a cross-sectional, single-center analysis of data collected from the validation sample of the PIDS.[27] Eligible participants with CD diagnosed according to international consensus criteria attending the Movement Disorders Clinic, University of Calgary, were consecutively recruited. Exclusion criteria included the inability to provide consent, dementia according to *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders*) criteria,[31] or disorders causing pain clearly unrelated to dystonia (eg, severe osteoarthritis/arthritis, malignancy). All participants provided informed consent. This study was approved by the University of Calgary Research Ethics Board (REB19-2111).

Participants were assessed clinically, obtaining their age, sex, and duration of dystonia. Data were collected within 14 days prior to the next scheduled botulinum toxin injection, at a mean ± standard deviation (SD) interval of 95 ± 7 days. They

completed the self-administered PIDS (Data S1),[27] which is comprised of 3 sections.

Section 1 measures *pain severity* at specific body parts (neck and shoulders, eyes, jaw, arms, legs, and mid/lower back), focusing on the week prior to the assessment. This section includes (1) pain intensity at its worst (0–10), (2) pain intensity on average (0–10), and (3) days × week with pain (adopting a rating from 0 to 3: 0 = no pain; 1 = <1 day/week; 2 = 2 to 4 days/week; 3 = >5 days/week). Section 1 subscores per body part are computed as follows: (pain intensity on average × 2 + pain intensity at its worst)/3 × days/week, generating a total subscore of 0 to 30. Section 1 subscores per body part are added to obtain the final score.

Section 2 measures the *functional impact* that pain has on 8 different activities: engaging in physical exercise, participating in social events and gatherings, completing household activities, driving, getting a good night's sleep or rest, doing outdoor leisure activities, working, and maintaining personal relationships. Responses are provided on a numerical scale from 0 to 3 (0 = no interference, 1 = sometimes interferes, 2 = often interferes, and 3 = unable to perform this due to pain), leading to a total score of 0 to 24. The pain-related functional impairment score of each participant is expressed in percentage of the total score to allow comparison with the scores from Section 3.

Section 3 evaluates the *external factors* that might trigger or relieve pain. Eight pain-triggering factors and 11 pain-Relieving factors are explored (see Data S1). Responses are provided on a numerical scale from 0 to 3 (0 = no effect or relief, 1 = mild effect or relief, 2 = moderate effect or relief, and 3 = severe effect or complete relief), leading to a total absolute score ranging from 0 to 24 for pain-triggering factors and from 0 to 44 for pain-relieving factors. Scores for both types of factors are expressed in percentage of the total score, as for functional impairment. Finally, to assess whether the modulation of pain from external factors was due predominantly to triggering or relieving factors, an index is calculated by subtracting the percentage score for pain-relieving factors from the percentage score for pain-triggering factors. The theoretical range of this *external factor index* is, therefore, between −100 and 100.

The median completion time was 10.4 min, with a range from 3.3 to 20.9 min, suggesting minimal burden for patients completing the scale after receiving basic instructions for self-administration. In addition, we administered the following:

- TWSTRS Psychiatric screening tool (TWSTRS-PSYCH),[26] consisting of 6 items assessing depression, loss of interest, discomfort, anxiety, physical symptoms of panic attack, and afraid of going outside (maximum total score 24).
- Global Dystonia Severity Rating Scale (GDRS),[32] as an instrument to assess dystonia severity. The total score is the sum of the scores for all the body regions (maximum total score 140).
- Craniocervical Dystonia Questionnaire-24 (CDQ-24),[33] evaluating quality of life in patients with CD and isolated blepharospasm. It includes 24 items based on 5 subscales (stigma, emotional well-being, pain, activities of daily living, and social/family life). Each item consists of 5 statements representing increasing severity of impairment, scored from 0 to 4 (maximum score 96).

## Sample Size and Statistical Analysis

Our study sample was the same as that involved in the validation of the PIDS and was calculated using an 8–10:1 sample-to-item ratio to Section 1 of the scale. Statistical analysis was performed using STATA, version 16. Descriptive data were expressed as mean and SD or percentage. We used a pairwise correlation analysis to measure the correlation between the 4 main scores generated by the 3 sections of the PIDS. Subsequently, we used age- and sex-adjusted linear regression models to estimate the relationship of pain-modulating factors to pain severity measured by Section 1 of the PIDS. Age- and sex-adjusted linear

**TABLE 1** *Demographic and clinical features of participants with isolated cervical dystonia*

| Demographic or clinical feature | Mean ± standard deviation or n (%) |
|---|---|
| Age at study period (yr) | 61.7 ± 10.1 |
| Females | 66 (77.7%) |
| Disease duration (yr) | 12.5 ± 10.5 |
| Global Dystonia Rating Scale (neck subscore) | 2.9 ± 1.5 |
| Global Dystonia Rating Scale (total score) | 4.8 ± 3.5 |
| Craniocervical Dystonia Questionnaire-24 total score | 27.8 ± 18.4 |
| Toronto Western Spasmodic Torticollis Rating Scale–psychiatric subscore | 5.8 ± 4.9 |
| Pain in Dystonia Scale Section 1 score | 17.8 ± 22.1<br>Median: 21.6<br>Interquartile range: 8.1–39.5<br>Full range: 0.4–125.5 |
| Medications in use (n, %) | |
| Botulinum neurotoxin | 78 (92%) |
| Clonazepam | 11 (13%) |
| Gabapentin | 3 (3.5%) |
| Trihexyphenidyl | 3 (3.5%) |
| Baclofen | 2 (2%) |
| Duloxetine | 1 (1%) |
| Oxycodone | 1 (1%) |
| Tramadol | 1 (1%) |
| Morphine | 1 (1%) |

regression models were also built to measure the impact of pain severity and other clinical variables on pain-related functional impairment (measured by Section 2 of the PIDS) and disease-specific quality of life (measured using the CDQ-24). The predetermined level of statistical significance was $P < 0.05$.

# Results

Our study population comprised 85 participants with CD, 66 of whom (77.7%) were women, with a mean ± SD age of 61.8 ± 10.1 years. Fifty-three (62.4%) had an associate, bachelor's, or graduate degree, whereas 32 of 85 (37.6%) did not complete any college degree. CD was focal in 94% and segmental in 6%. Ninety-two percent were treated with botulinum neurotoxin A. Median, interquartile range, and full range of the PIDS pain severity score were 21.6, 8.1 to 39.5, and 0.4 to 125.5. Additional clinical features, including medication use, are presented in Table 1. The body distribution of pain is shown in Figure S1; 11 of 85 participants (12.9%) reported pain exclusively in the neck, 2 of 85 (2.4%) exclusively in body parts other than neck, and 56 of 85 (65.9%) in the neck and at least another body part.

Among the 8 factors explored as potential pain triggers, stress (both physical and emotional) and prolonged fixed position were the most frequently reported and impactful, followed by changes in posture and exercise, the latter including any type of physical exercise that encompasses sports activities, activities performed at a gym or with gym equipment, or exercises prescribed by a personal trainer or physiotherapist. Figure 1 shows the effect rating related to these factors. The effect of potential pain-relieving factors was mild in more than 50% of participants for 9 of the 11 factors assessed (see Fig. 2 for details). Self-prescribed treatments (over-the-counter medications or complementary/alternative medicinal products that do not require prescription from health professionals) and alcohol were reported to exert mild relief on pain by only 42.4% and 25.9% of participants, respectively; 52.9% and 49.4% of participants reported no use of these methods of pain control. Four factors were listed among both triggering and relieving factors: heat or cold or both (reported having both types of effect by 38 [44.7%] patients), changes in posture (reported having both types of effect by 57 [67%] patients), and exercise and manipulation/massage—the latter intended as a form of intervention administered by a physiotherapist, massage therapist, or chiropractor—(each reported having both types of effect by 34 [40%] patients). The percentage

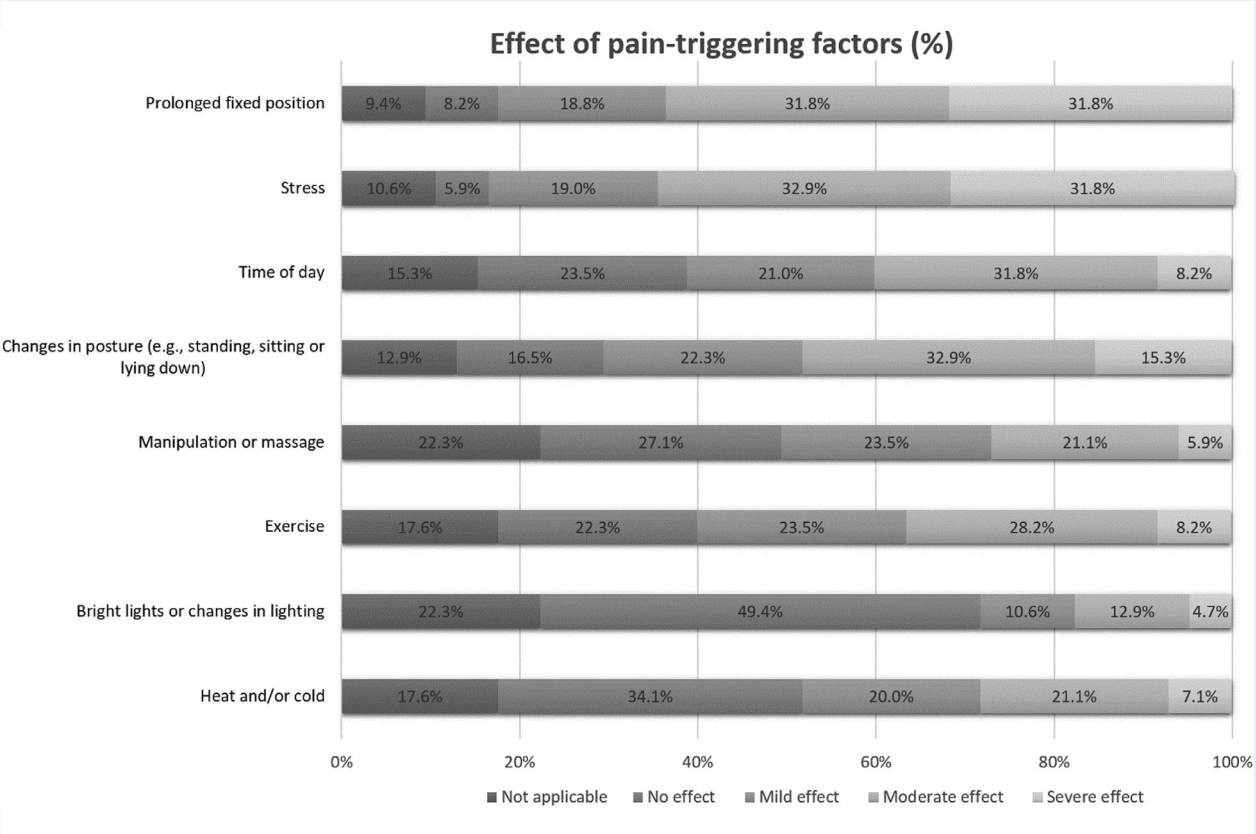


FIG. 1. Prevalence and effect of external pain-triggering factors in isolated cervical dystonia assessed using Section 3 of the Pain in Dystonia Scale (PIDS).

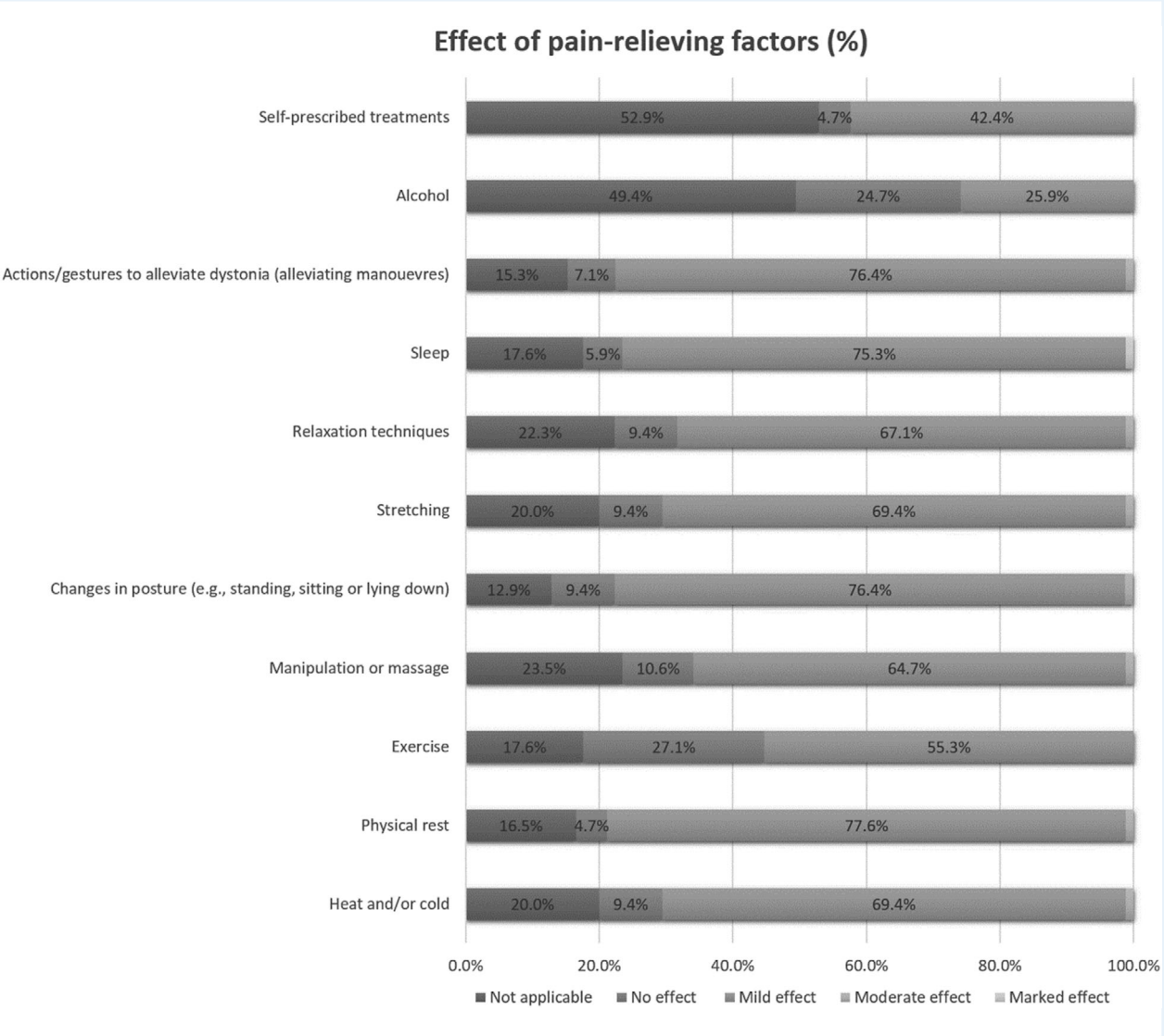


**FIG. 2.** Prevalence and effect of external pain-relieving factors in isolated cervical dystonia assessed using Section 3 of the Pain in Dystonia Scale (PIDS).

total score of pain-triggering factors was significantly higher in women ($40.9 \pm 22.9$) than in men ($26.3 \pm 24.3$, $P = 0.02$), whereas the difference between women and men in percentage total score of pain-relieving factors ($22.2 \pm 10.1$ vs. $17.7 \pm 12$) was not significant ($P = 0.1$).

Pain was highly impactful in most participants (Fig. 3). Pain interfered with engaging in physical exercise in 71.9% and with participating in social events and gatherings in 71.8%. Getting a good night's sleep or rest was affected by pain in 65.9% of participants, completing household activities in 65.8%, and outdoor leisure activities in 62.3%. More than half of participants reported functional interference of pain also on driving, working, and personal relationships.

Pain severity score correlated positively with both pain-triggering factors and pain-relieving factors in percentage total scores (Table 2). The percentage total scores of pain-triggering and pain-relieving factors showed very high positive correlation (Table 2). Both percentage total scores of pain-triggering and pain-relieving factors were highly positively correlated with the number of body parts (range: 0–6) in which pain was reported ($r = 0.58$, $P < 0.0001$; $r = 0.52$, $P < 0.0001$, respectively). The external factors index showed greater effect of pain-triggering factors (ie, positive value) in 65 of 85 (76.5%), greater effect of pain-relieving factors (ie, negative value) in 11 of 85 (12.9%), and complete balance between pain-triggering and pain-relieving factors (ie, 0 value) in 9 of 85 (10.6%). The external factor index also positively correlated with pain severity score ($r = 0.34$, $P = 0.01$). Age- and sex-adjusted linear regression models indicate that higher total percentage scores of pain-triggering factors and pain-relieving factors, as well as index for external pain-

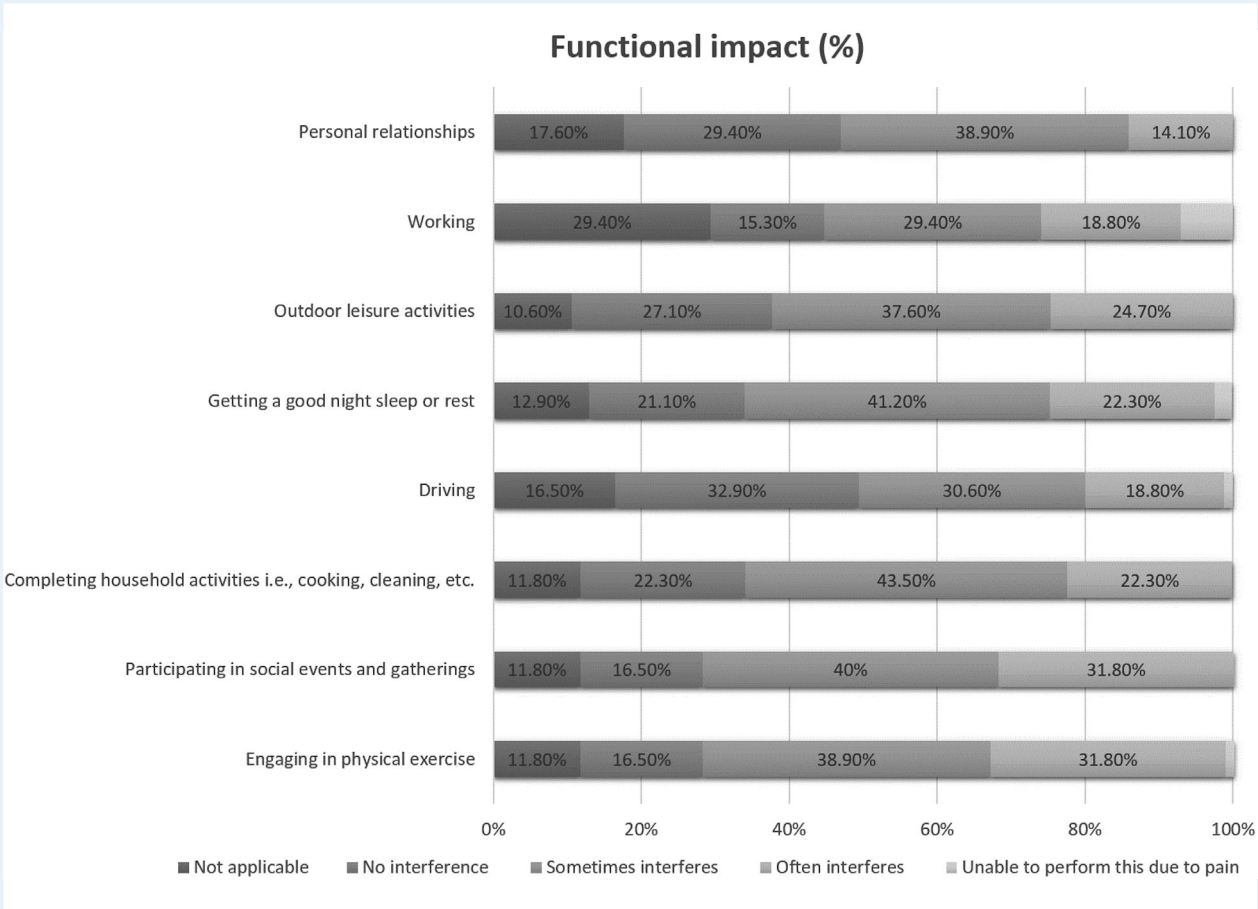


**FIG. 3.** Pain-related functional impact on routine daily activities in isolated cervical dystonia assessed using Section 2 of the Pain in Dystonia Scale (PIDS).

modulating factors, all significantly predicted higher pain severity scores (Table 3); none of the demographic and other clinical variables influenced these predictive effects.

Pain-related functional impairment score and pain severity score were positively and significantly correlated (Table 2). Age- and gender-adjusted linear regression shows that higher pain severity score, GDRS neck subscore, and TWSTRS-PSYCH score all significantly predicted higher pain-related functional impairment scores (Table 4); none of the demographic and other clinical variables explored influenced these predictive effects.

Finally, higher CDQ-24 quality-of-life total scores were significantly predicted by higher pain severity scores, higher pain-related functional impairment scores, and higher TWSTRS-PSYCH scores, but not by higher GDRS neck

**TABLE 2** *Pairwise correlation analysis of the different scores of the PIDS*

| | PIDS pain severity score | PIDS triggering factors score | PIDS relieving factors score | PIDS pain-related functional impairment score |
|---|---|---|---|---|
| PIDS pain severity score | 1.00 | | | |
| PIDS pain-triggering factor percentage score | 0.38* | 1.00 | | |
| PIDS pain-relieving factor percentage score | 0.28* | 0.72* | 1.00 | |
| PIDS pain-related functional impairment score | 0.41* | 0.81* | 0.66* | 1.00 |

*Note*: Numbers express correlation coefficients. *Statistical significance at the $P < 0.05$ level for the corresponding correlation coefficient.
Abbreviation: PIDS, Pain in Dystonia Scale.

**TABLE 3** *Linear regression models estimating the relationship between pain-modulating factors and the PIDS severity score (dependent variable)*

| | β Regression coefficient | P | 95% Confidence interval |
|---|---|---|---|
| PIDS pain-triggering factor percentage subscore | 0.31 | 0.002 | 0.12–0.50 |
| PIDS pain-relieving factor percentage subscore | 0.49 | 0.03 | 0.06–0.92 |
| PIDS global external pain-modulating factor percentage subscore | 0.22 | 0.002 | 0.08–0.36 |
| Triggering-relieving score (ie, skewness index for external pain-modulating factors) | 0.37 | 0.006 | 0.11–0.63 |

*Note*: All estimates are age- and gender adjusted.
Abbreviation: PIDS, Pain in Dystonia Scale.

subscores or higher pain-triggering and pain-relieving factor scores (Table 5).

# Discussion

Our study explored data collected from the recently developed PIDS instrument to investigate the external modulation of pain and the relationship between pain severity, pain-related functional impairment, quality of life, and other clinical features in a representative sample of patients with CD. The subjectively reported effect of extrinsic pain-triggering factors was proportionately larger than that of extrinsic pain-relieving factors, confirming the major impact of pain on personal, social, and occupational activities. Pain-related functional impairment was independently influenced by the severity of pain, dystonia, and depressive/anxiety symptoms, whereas quality of life was predicted more by pain severity, pain-related impairment, and psychiatric symptoms than by dystonia severity.

The effect size of pain-triggering factors was higher in female participants. The greater representation of women in CD in our sample, aligned to the female-to-male ratio in the general patient population,[34] may have contributed to this. Even if the effect size of pain-triggering factors was greater than that of pain-relieving factors, their percentage scores show a strong positive correlation. This suggests that mechanisms underlying subjective reporting of triggering and relieving factors may partially overlap. Moreover, higher scores for either of these modulating factors predict higher pain severity. Lower pain acceptance, besides being associated with a higher perception of pain intensity in CD,[24] may be associated with a higher perception of pain being susceptible to external factors. This aligns well with the high interindividual variability of pain experience in both general population[35] and CD patients. Pain-triggering factors might worsen dystonic muscle contractions, thus contributing to worsening of pain. In addition to sex, genetic and psychosocial variables—not explored here—could moderate how the environment influences pain in CD. The coexistence and complexity of pain types affecting individuals with CD could also lead to differences in external modulation between different pain types. Finally, an alternative intriguing explanation for this finding is that the relatively smaller effect of pain-relieving factors reflects the deficit of inhibitory pain mechanisms previously documented in CD.[23]

The effect size differs substantially across the pain-triggering factors we investigated. Both emotional (stress) and physical (prolonged fixed position, changes in posture, exercise) factors play a moderate or major effect, supporting multifactorial pain modulation in CD. The relationship between emotional stress and pain is well established,[36] although future research should elucidate whether specific stressors exert a greater impact on pain in this clinical population. This finding supports stress management interventions in CD to target not only anxiety and dysregulated mood but also the experience of pain. Both fixed positions and postural changes can trigger or aggravate pain in CD, and this can also be due to spondylodegenerative changes associated with CD.[37] Whereas a link between pain and prolonged fixed positions is intuitive, the relationship to postural changes implies an increase in compensatory muscle contractions countering dystonia. This supports using physiotherapy to improve pain in CD,

**TABLE 4** *Linear regression models estimating the relationship between clinical variables and the PIDS pain-related functional impairment subscore (dependent variable)*

| | β Regression coefficient | P | 95% Confidence interval |
|---|---|---|---|
| PIDS pain severity subscore | 0.06 | 0.005 | 0.02–0.10 |
| Global Dystonia Rating Scale (neck subscore) | 0.72 | 0.01 | 0.16–1.28 |
| Toronto Western Spasmodic Torticollis Rating Scale -psychiatric subscale | 0.44 | <0.001 | 0.25–0.62 |

*Note*: All estimates are age- and gender adjusted.
Abbreviation: PIDS, Pain in Dystonia Scale.

**TABLE 5** *Linear regression models estimating the relationship between clinical variables and the Craniocervical Dystonia Questionnaire-24 score (dependent variable)*

| | β Regression coefficient | P | 95% Confidence interval |
|---|---|---|---|
| PIDS pain severity subscore | 0.14 | 0.02 | 0.02–0.25 |
| PIDS pain-triggering factor percentage subscore | −0.003 | 0.98 | −0.18 to 0.18 |
| PIDS pain-relieving factor percentage subscore | −0.001 | 0.99 | −0.32 to 0.31 |
| PIDS pain-related functional impairment subscore | 1.09 | 0.02 | 0.21–1.97 |
| Global Dystonia Rating Scale (neck subscore) | 1.2 | 0.13 | −0.37 to 2.76 |
| Toronto Western Spasmodic Torticollis Rating Scale -psychiatric subscale | 2.06 | <0.001 | 1.50–2.61 |

*Note*: All estimates are age- and gender adjusted.
Abbreviation: PIDS, Pain in Dystonia Scale.

although physiotherapy programs for this condition are not standardized and high-quality evidence of their usefulness is lacking.[38,39] A recent single-center observational study showed that higher pain severity in CD is associated with higher use of physiotherapy, encompassing different treatment forms (exercise to decrease muscle tone or to correct abnormal postures), with an average improvement of pain of 51% when receiving it.[40] Finally, an unexpected finding is the relatively large pain-triggering effect of the time of day, which may be related to physical fatigue and deserves further exploration.

Across the pain-relieving factors captured by the PIDS, the effect on pain was similar and predominantly mild, suggesting nonspecific influences of extrinsic factors on pain alleviation in CD. Several factors appear as both triggers and relieving factors in a proportion of patients. This applies particularly to exercise and postural changes, suggesting the need to better explore the relationship between pain (and likely other clinical features of CD) and activity-related factors. The effect of exercise on the intensity of dystonia-related symptoms varies considerably between light and strenuous exercise.[40,41] The PIDS section exploring pain-modulating factors was not designed to analyze these influences in depth but rather to guide clinical evaluation toward specific factors that can influence pain at an individual level. About three-quarters of patients reported that sleep can relieve pain to a mild degree, which suggests a potential interaction between sleep disruption and pain severity, in line with the conceptualized interrelatedness of nonmotor features in CD.[1,24,42] Therefore, a small polysomnography study showed that sleep and resting in a supine position could reduce neck pain by about 50%.[43] A bidirectional relationship between pain and sleep disruption in CD is suggested by the observation that two-thirds of our patients reported a relevant impact of pain on nighttime sleep quality. This is in line with the finding that sleep impairment and pain catastrophizing co-segregate in cluster analyses from independent cohorts of CD patients.[24] Of 40 patients resorting to self-prescribed treatments for pain (eg, over-the-counter analgesics), none reported moderate or marked relieving effect of these treatments, confirming that common analgesics may not be sufficient to counteract pain in CD. Finally, the effect of alleviating maneuvers for CD was rated as mild by 76.4% of participants. The relationship between pain and alleviating maneuvers in CD is complex, with a previous study reporting a direct association between the presence of an effective sensory trick and the presence of pain.[4] Although pain may increase patients' focus on identifying an effective alleviating maneuver, our finding suggests that the latter does not exert a relieving effect on pain greater than other external factors.

The pain-related functional impairment section of the PIDS confirms the broad impact of pain in CD. In most patients, this functional impairment was mild to moderate, and complete inability to perform routine activities due to pain was very rare. Our linear regression analysis shows that the functional impairment due to pain is related independently to pain severity, severity of motor symptoms, and severity of depressive/anxiety symptoms. The observation of an apparently independent, direct relationship between the severity of motor symptoms and pain-related impairment is probably a result of the relevant causal contribution of motor symptoms to pain in CD. More importantly, psychiatric symptom severity appears to be the strongest predictor of pain-related impairment, which is in line with a greater perception and catastrophic interpretation of pain in people with a larger burden of depressive and anxiety symptoms.[24,44] Moreover, psychiatric features are another important feature co-segregating with disrupted sleep quality and pain catastrophizing in the cluster analyses from the Dystonia Coalition and Dystonia Wales cohorts cited earlier.[24]

We were able to confirm the greater predictive effect of common nonmotor symptoms on health-related quality of life, measured using a validated disease-specific instrument (CDQ-24). Both severity and related impairment from pain were independent predictors of quality of life, whereas psychiatric symptoms were confirmed as the greatest predictor of quality of life in CD. It is noteworthy that the CDQ-24 includes 6 questions on emotional well-being and 3 on pain,[33] which may also have contributed to the predictive effect of pain and psychiatric features on quality of life in our study population. Conversely, in the same regression model, the neck subscore of the GDRS was not a significant predictor of quality of life.[2,5]

Our study has noteworthy limitations. The PIDS instrument was conceived as a rating scale evaluating pain across the whole spectrum of AOID in a mechanism-agnostic fashion, collecting information on pain across different body regions. Sections 2 and 3 were developed to guide clinicians toward understanding pain susceptibility to external factors and functional impact on an individual basis, but their numerical rating system was not included in our previous validation study of the PIDS. Therefore, the analysis presented here represents a post hoc exploration of data collected through an instrument developed primarily for clinical purposes. Another limitation is the restricted number of modulating factors and functional activities included in the PIDS, which may have missed others that could have been relevant to a proportion of our patients. This limitation is mitigated by the fact that the development of each section of the PIDS involved multiple iterations within an international group of experts and piloting from patients.[27] Even if we built regression models to assess the predictive effects of clinical scores, the observed the relationship cannot be seen as a demonstration of cause–effect relationship between independent and dependent variables, and ad hoc studies should be conducted to explore the mechanistic basis of these relationships. The relatively limited sample size prevented us from assessing the co-clustering of the effect of modulating factors, which might have suggested the involvement of specific mechanisms underlying pain in CD. Finally, the cross-sectional design of our study did not allow us to investigate the relationship between external modulation of pain and the pain-relieving effect of botulinum toxin injections, which would justify the use of the PIDS in future prospective studies.

In conclusion, our study shows that the PIDS is a composite clinical rating instrument that not only is valid for pain severity rating but can also inform on external modulation and functional impact of pain in patients with CD. The pattern of external modulation described here supports the multifactorial modulation and complex underlying physiology of pain in CD. New studies on larger sample sizes using the PIDS could shed light on the co-segregation of extrinsic pain-modulating factors and their relationship to other common nonmotor features of CD, particularly depression, anxiety, and sleep disruption. Finally, the potential variety and overlap of pain types, including musculoskeletal pain, neuropathic pain, and various forms of headache, add to the complexity of this symptom in CD and require further exploration.

# Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical analysis: A. Design, B. Execution, C. Review and critique; (3) Manuscript: A. Writing of the first draft, B. Review and critique.

D.M.: 1A, 2A, 2B, 3A
B.M.C.A.: 1B, 1C, 2C, 3B
F.M.: 1C, 3B
R.E.: 1C, 3B
S.H.F.: 1C, 3B
A.S.: 1C, 3B
M.S.: 1C, 3B
M.J.E.: 1C, 3B
S.A.-C.: 1C, 3B
G.D.: 1C, 3B
K.R.-C.: 1C, 3B
K.P.-D.: 1C, 3B
S.P.R.: 1C, 3B
H.A.J.: 1C, 3B
V.B.: 1A, 1B, 2C, 3B

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# Disclosures

**Ethical Compliance Statement**: This study was approved by the University of Calgary Research Ethics Board (REB19-2111). All participants signed a written informed consent, which has been securely stored in an encrypted folder at the University of Calgary. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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She is a member of the MDS-UPDRS Development Group, the MDS-NMS Development Group, the NINDS CDE QoL Group, the MDS Rating Scales Review Committee, and the MDS COA Early and Prodromal PD Working Group. Dr. Schrag has been involved in the development of the MDS-UPDRS, the MDS-NMS, and the PQoL. She reports consultancy fees from Biogen, AbbVie, Roche, Bial, and GE Healthcare; license fees from the University College London; and royalties from the Oxford University Press. Dr. Maria Stamelou is head of Parkinson's Disease and Movement Disorders Department, "HYGEIA" Hospital, Athens, Greece, and professor at Philipps University, Marburg, Germany, and the European University of Cyprus. Dr. Silke Appel-Cresswell has received honoraria for consulting and speaking from Merz and AbbVie and is site PI for clinical studies by AbbVie and Praxis. 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## Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. ■

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# Supporting Information

Supporting information may be found in the online version of this article.

**Figure S1.** The figure reports the frequency of pain based on anatomical distribution in our clinical sample of patients with cervical dystonia (see also reference 27).

**Data S1.** The file contains the complete version of the Pain in Dystonia Scale, previously published in reference 27.