

## When movement disorders hurt: Addressing pain in hyperkinetic disorders

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### Abstract

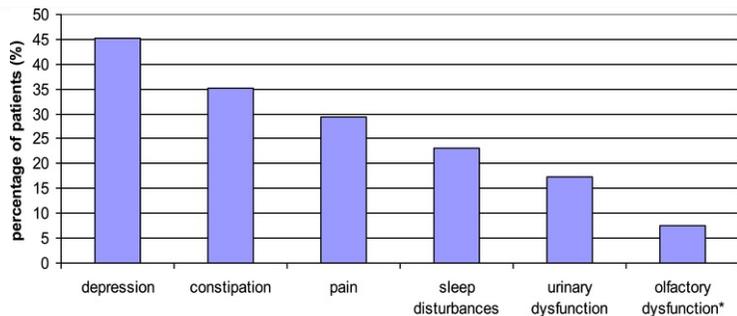
Pain is an important nonmotor symptom in movement disorders. Dystonia is a hyperkinetic movement disorder characterized by involuntary, sustained or intermittent muscle contractions causing abnormal movements, postures or both. Contrary to common views the nonmotor symptoms are present in dystonia patients. Pain is a prevailing feature of cervical dystonia (CD), the most common form of focal dystonia. The mechanism of pain in CD remains mostly unknown, but there are growing evidence that it could not be only the consequence of muscle hyperactivity. We have shown that botulinum toxin (BoNT) produced pain relief before muscle relaxation and that effect on pain relief lasted longer than the effect on motor improvement. More and more data suggest that pain relief could be attributed to the direct effect of BoNT type A on central nervous system. Pain, depression, and anxiety have been shown to be significant determinants of QoL in focal dystonia patients. Routine clinical examination in patients with dystonia should include evaluation of motor as well as non-motor symptoms. Selective rating assessment should be used in clinical practice to quantify pain. Specific assessment of pain is important to determine the effect of BoNT as the most effective treatment in focal dystonia.

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**Keywords:** Dystonia; Non-motor symptoms; Pain; Botulinum toxin

## 1 Introduction

For a long time the most common accepted criteria for the diagnosis of movement disorders were associated with motor symptoms only. The best example is Parkinson's disease (PD). However, already James Parkinson noted that in addition to dominant motor signs, the presence of other symptoms, such as sleep disorder, pain, and gastrointestinal dysfunction [1,2] is important as well. In spite of such non-motor (NMS) symptoms, signs such as tremor, slowness of movement, and gate disturbances, have dictated clinical management and research in PD. In the last few decades, we have become more aware not only of the frequency of NMS in PD but of the great impact of such symptoms on patient disability and quality of life (QoL) [3]. The most common NMS in the early stage of the disease are hyposmia, pain and sleep disturbances [4]. Pain, depression and anxiety are clearly associated with worsening of QoL [4,5]. Pain in PD patients can precede motor symptoms by several years [6,7]. Pain was the third most common NMS in our preliminary research of de-novo untreated PD patients (Fig. 1.) Classification of pain related to PD includes different categories such as musculoskeletal, dystonic, neuropathic/radicular, central or primary pain and akathisia [8]. Contrary to PD, pain in dystonia was considered to be a consequence of muscle hyperactivity and/or contraction. Dystonia, as a third most common movement disorder, is typically defined as a hyperkinetic syndrome of sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both [9,10]. Dystonic movements are typically patterned, twisting, worsened by voluntary action, and may be tremulous. However, growing evidence indicates an important non-motor spectrum of symptoms in patients with dystonia including neuropsychiatric, cognitive, and sleep problems, as well as abnormalities in sensory function [11]. In addition, mild sensory symptoms such as discomfort in the neck before occurrence of motor signs in cervical dystonia (CD), and irritation or dry eyes prior to the development of blepharospasm have been reported.



**Fig. 1** Prevalence of nonmotor symptoms in 56 drug naive PD patients.

Data represent percentage (%) of total number of patients (n = 56).

\*Anamnestic data without quantitative testing.

alt-text: Fig. 1

## 2 Pain in cervical dystonia

Pain is a prevailing feature of CD, the most common form of focal dystonia [12,13]. Pain, depression, and anxiety have been shown to be significant determinants of QoL in patients with focal dystonia. Preliminary results of our ongoing study investigating prevalence of NMS in CD patients are summarized in Table 1. Previously untreated CD patients (n = 36) had significantly higher score on Bodily Pain domain of the SF-36, as well as higher incidence of depression (Beck Depression Inventory, 2nd edition - BDI-II) and anxiety (Beck Anxiety Inventory-BAI) compared to gender and age-matched asymptomatic control subjects. The high incidence of pain in CD contributes significantly to the patients disability and low QoL. In some studies up to 90% of patients reported pain associated with CD [14]. A recent multicenter study showed that 88.9% of patients reported pain associated with CD, and 70.7% rated their pain as moderate or severe [15]. According to some studies, pain is the main reason for patients to seek treatment for CD [16]. The role of pain in CD pathophysiology and severity is not well understood. Relationship between pain in CD and disease severity is complex. Usually, it was thought that pain is a consequence of increased severity of dystonia and muscle spasm or hyperactivity. It may seem obvious that dystonic muscles would be painful, but not all the patients with similar degrees of dystonia report equal amounts of pain. Although degree of head deviation and muscle tension may correlate with pain level, somewhat surprisingly, the objective severity of neurologic signs has not. One potential reason that pain is so prevalent in dystonia is that the threshold for experiencing pain may be reduced [17]. Patients with dystonia may also have alterations in pain processing, even in body parts without dystonic involvement.

**Table 1** Demographic and baseline clinical characteristics of patients with cervical dystonia before treatment and control group.

alt-text: Table 1

	CD	Control group	p value
Number (Male/Female)	36 (16/20)	57 (24/33)	
Mean age (SD)	46.8 (10.7)	46.3 (12.4)	>0.05
Age of onset (SD)	44.3 (10.8)	NA	NA
Disease duration (SD)	2.4 (1.9)	NA	NA
Education (SD)	13.4 (2.60)	13.7 (2.4)	>0.05
SF-36 - Bodily pain (SD)	53.9 (21.4)	78.7 (18.6)	<0.001
TWSTRS (SD)	31.3 (5.7)	NA	NA
TWSTRS - pain subscale (SD)	6.7 (3.9)	NA	NA
BAI (SD)	13.6 (6.7)	7.7 (5.1)	<0,001

BDI (SD)	12.6 (6.1)	6.2 (4.6)	<0.001
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SD, standard deviation; SF-36, 36-Item Short Form Health Survey; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; NA, not applicable.

Alterations in the somatosensory system have been documented in patients with focal or generalized dystonia. In addition to electrophysiological studies, neuroimaging studies support the hypothesis of reduced intracortical inhibition not only to the motor cortical level but also somatosensory cortex [18]. In future, the pathophysiology of the non-motor symptoms in dystonia should be investigated in addition to motor symptoms. Clinical examination should include motor as well as non-motor status in patients with dystonia.

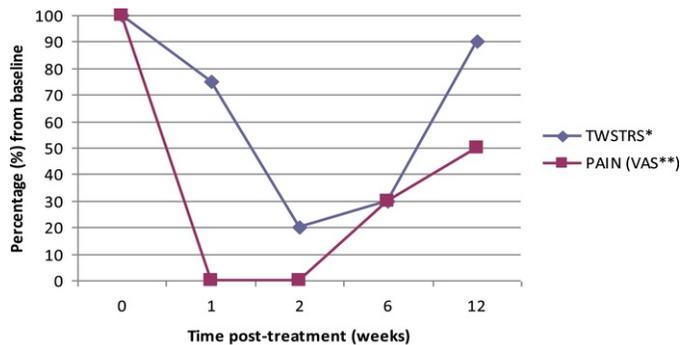
### 3 Pain assessment in cervical dystonia

Several scales have been used to evaluate CD, incorporating both objective and subjective measures. The most widely used is the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) [19] along with the Burke-Fahn-Marsden Dystonia Scale [20] and the Tsui Scale [21]. The TWSTRS (range 0-85 points) consists of three subscales: severity (range 0-35), disability (range 0-30) and pain (range 0-20). It is valid and sensitive to changes in CD [16]. The Burke-Fahn-Marsden Dystonia Scale consists of two sub-scores (movement and disability). The Tsui Scale is composed of four sub-scores (movement, duration, shoulder elevation and tremor). Only the TWSTRS covers pain, and none assesses QoL. The TWSTRS pain sub-scale consists of a severity score for the patient's usual, worst and best pain in the previous week, as well as a duration component and an assessment of the contribution of pain to disability [22]. Pain in patients with CD has mostly been evaluated using self-assessment analogue scales and the TWSTRS pain subscale [23,24].

### 4 Pain and botulinum toxin in the treatment of cervical dystonia

Therapeutic options for CD could be divided into botulinum toxin (BoNT), oral analgesic medication, functional neurosurgery (DBS) and physical therapy. There are limited data of oral medication in CD. Anticholinergics were the most prescribed in clinical practice mainly before the introduction of BoNT. There are no specific controlled clinical trials of anticholinergics in CD. Only one small trial compared BoNT versus trihexyphenidyl in CD. Brans et al. reported BoNT to be superior to trihexyphenidyl in pain relief [25].

BoNT is the treatment of choice for CD. Its efficacy and safety is well-established as an effective and first line treatment in CD according to several class I studies [26]. Currently, two serotypes are used (BoNT type A and BoNT type B). Four brands of BoNT are approved for the treatment of CD. There is weak evidence suggesting significant difference in efficacy and safety between different brands. Systemic review of the current literature has supported the usage of BoNT as the most effective treatment for reducing dystonic symptoms and pain in patients with CD [27]. However, for a long time pain assessment was not specifically targeted in clinical trials with BoNT. In addition, it was widely accepted that pain in patients with focal dystonia is a consequence of sustained muscle contraction. Thus, it is considered that BoNT treatment attenuates pain by symptomatic muscle relaxation. Many randomized controlled trials used the Tsui scale as outcome measure to evaluate BoNT efficiency [21], indicating a limitation because the pain item is not incorporated in this scale. But, as presented on Fig. 2, when using Visual Analogue Scale (VAS) we found that in CD patients the effect of BoNT type A on pain relief was evident before muscle relaxation and motor improvement (TWSTRS motor score). Effect on pain also lasted longer than the effect on motor improvement. Our results are in line with published studies where pain relief was assessed using an analogue scale [15,28]. They showed that pain relief was not associated with usual muscle relaxation dose of BoNT [28]. More and more data indicate that mechanisms other than muscle weakening contribute to pain relief after BoNT injections. Today, there are no doubts that BoNT involves central effects, suggesting that pain relief could be attributed to the direct effect on central nervous system [29]. In the motor system BoNT action was attributed to its well-known peripheral anticholinergic action in neuromuscular junctions. However, after peripheral injections in rodents the enzymatic activity of BoNT type A was recently immunohistochemically detected in motor and sensory regions of brain stem and spinal cord [30]. In sensory regions, the function of BoNT activity is associated with its antinociceptive effects, while in motor regions we are only aware of its presence. Physiological and/or behavioral effects of BoNT A in central motor system after peripheral injections are yet to be determined in future studies. In clinical practice, it is important to include motor and nonmotor status examination, as well as QoL in dystonia patients to establish the selective and specific effects of different treatments.



**Fig. 2 Clinical Effects of Botulinum Toxin Type A in Spasmodic Torticollis: TWSTRS and Pain Severity.**

Data represent changes from baseline in percentage (%) in total TWSTRS\* (Toronto Western Spasmodic Torticollis Rating Scale) score and pain score measured by Visual analogue scale (VAS\*\*) before treatment with botulinum toxin type A and during 12 weeks follow up in 20 CD patients.

alt-text: Fig. 2

## Documentation of author roles

M Relja, V Miletić (Drafting the manuscript).

M Relja (Critical revision of the manuscript for important intellectual content).

M Relja, V Miletić, (Acquisition of data).

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## Conflicts of interest

None.

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### Highlights

- Non-motor symptoms are increasingly recognised in patients with dystonia.
  - Pain is a prevailing non-motor feature in patients with CD and significant determinant of QoL.
  - Clinical examination in patients with dystonia should include evaluation of motor as well as non-motor symptoms.
  - Treatment with BoNT significantly reduces pain.
  - There are growing evidence on central mechanism of BoNT induced pain relief.
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## Queries and Answers

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