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Optimization of pain management in cervical dystonia

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ABSTRACT

Cervical dystonia (CD) is the third most common movement disorder characterized by sustained or intermittent muscle contractions causing abnormal movements, postures, or both. Pain in the course of CD is a frequent symptom reported by the 54.6% - 88.9% of patients, which strongly affects the disability and quality of life, and is the most common reason patients are looking for treatment. Despite the main effect of botulinum toxin (BoNT) is muscle relaxation through the inhibition of the acetylcholine release at the neuromuscular junction, the analgesic effect of BoNT is probably attributed to the acting on central nervous system. Up to 20% of patients discontinue therapy due to treatment failure or adverse effects. Most poor responses are related to suboptimal treatment and a minority to immunoresistance which currently concerns only 0-2,5% of CD cases. In case of confirmed immunoresistance to BoNT-A standard therapy, the use of BoNT-B or alternative BoNT-A is recommended. The currently available management of improving the analgesic efficacy of first-line treatment in patients without immunoresistance includes: the eradication of BoNT adverse events, the determination of individual BoNT dosage, reviewing injections technique with electromyography or ultrasound guidance, the implementation of a rehabilitation program and

the applying of the invasive or non-invasive brain stimulation methods. However, due to the lack of evidences from the large, randomized, controlled, clinical trials, an issuance of unambiguous recommendations remains difficult. Further studies on a poor response to BoNT injections and analgesic effects of above methods in the treatment of the CD-related pain are needed.

***Keywords*:**
Cervical Dystonia, Torticollis, Pain, Botulinum Toxins.

INTRODUCTION

Cervical dystonia (CD) is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal movements, postures, or both, which involve the same parts of the body. The above mentioned movements symptoms are usually repetitive, stereotyped, involuntary, and aggravated by voluntary action [1]. CD is the third most common movement disorder with the estimated prevalence ranges from 57 to 280 people per million [2].

Currently CD is considered as a tripartite disorder, with motor, affective, and subtle cognitive features [3]. Among the determinants of the quality of life, physical, social and emotional aspects are the most affected [4].

The frequency of the pain occurrence accounts for 54.6% - 88.9% of the patients with CD. Despite the most frequent symptoms contributing to the disability are the motor one, pain is the most disabling non-motor symptom, which provides an additional source of impairment and strongly attributes to the quality of life deterioration [5]. In addition, patients report pain as a main reason they are searching for treatment [6]. Body regions commonly affected by the pain in CD are the head, neck, and the ipsilateral arm on the rotation side of the head [7].

The pathogenesis of pain

Formerly pain reduction was perceived as a direct result of muscle contraction only. Currently we know that non-motor symptoms, include pain, may not be directly attributed as a secondary consequence of motor symptoms. Despite the fact that the level of pain correlates with the degree of head deviation and subjective muscle tension, neither patients with the objective severity of neurologic signs nor with the similar degrees of dystonia report equal amounts of pain [7]

There are three possible theories for the pain presence observed in CD. Firstly, pain may occur a result of the central processing of nociceptive stimuli alterations at the spinal level [5]. Secondly, the central serotonergic system defect were found in CD patients which CD. In one of the most recent study, higher presynaptic serotonin transporter binding were considered to play role in the pathophysiology of pain as well as other non-motor and motor symptoms [8]. Thirdly, the pain experiencing threshold is reduced in patients with CD compared to healthy controls. Reduced pain-pressure thresholds were also reported from non-affected muscles due to possible alterations in pain processing [7].

Scales used in pain evaluation

The Movement Disorders Society selected two scales as the most valuable with regard to clinimetric properties: the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) and the Cervical Dystonia Impact Profile (CDIP-58) [9]. TWSTRS include three subscales for the assessment of CD-related severity, disability and pain. Points in pain subscale are assigned for the pain severity (0-10), duration (0-5) and disability (0-5) [10]. CDIP-58 consists of 58 items and includes patients' perceptions and complements without separating any special part for the pain assessment only. The main target of this scale is to measure the health impact of CD in eight health dimensions [11]. The simplest scale used in clinical practice is the Pain Numeric Rating Scale (PNRS) originating from the Visual Analog Scale (VAS). Patients are asked to choose a whole number from the range from 0 to 10 which correlate with pain severity (0 refers to the absence of pain and 10 refers to the worst imaginable pain) [12].

In 2015, Comella et al. established a new scale used in the assessment of CD named Comprehensive Cervical Dystonia Rating Scale (CCDRS). CCDRS consists of the components originating in three previously implemented scales:

1. TWSTRS-2 as a modification of TWSTRS supplemented by the variable items scaling, without an item for head tremor and the weighting of the duration factor by two,
2. TWSTRS-PSYCH for the assessment of the psychiatric disorders associated with CD,
3. CDIP-58 which was applied in its original form [13].

The CCDRS may be useful in pain evaluation, however, the application of this scale in clinical studies is still lacking [5,14].

PAIN TREATMENT WITH BOTULINUM TOXIN

Current recommendations

The main effect of botulinum toxin (BoNT) is the inhibition of acetylcholine release at the neuromuscular junction. The European Federation of Neurological Societies recommends BoNT injections as a safe, efficacious and first choice treatment for CD. The treatment cycles can be repeated over many years [15]. Generally, there are two types of BoNT: type A and type B. The American Academy of Neurology support the use of two types of BoNT as established as effective with the level A recommendation: abo-botulinum toxin A (abo-BoNT-A) and rima-botulinum toxin B (rima-BoNT-B). There are also two other types of BoNT with the level B recommendation: ona-botulinum toxin A (ona-BoNT-A) and inco-botulinum toxin A (inco-BoNT-A) [16]. Types A and B appear to be equally effective and safe in the treatment of adults with certain types of cervical dystonia and should be injected in the strictly defined doses summarized in table 1 [17,18].

Table 1. Muscles commonly affected in CD, their function and BoNT doses [17].

	Muscle	Function	BoNT dose
ANTERIOR	Longus collis	Flexion (forward) Mild rotation (ipsi)	BoNT-A/Ona/Inco:15-30 U BoNT-A/Abo: 20-60 U
	Longus capitis	Flexion (forward) Rotation (ipsi)	BoNT-A/Ona/Inco: 5-15 U BoNT-A/Abo: 20-60 U
	Rectus capitis anterior	Flexion (forward)	BoNT-A/Ona/Inco: 2,5-10 U BoNT-A/Abo: 10-30 U
	Sternocleidomastoid	Rotation (contra) Tilt (ipsi) Sagittal shift (backward) Flexion (forward)	BoNT-A/Ona/Inco: 20-50 BoNT-A/Abo: 40-120 BoNT-B/Rima: 1,000-3,000
LATERAL	Anterior scalene	Tilt (ipsi) Rotation (contra) Flexion (forward)	BoNT-A/Ona/Inco: 5-30 BoNT-A/Abo: 20-100 BoNT-B/Rima:500-2,000
	Middle scalene	Tilt (ipsi) Rotation (contra)	BoNT-A/Ona/Inco: 5-30 BoNT-A/Abo: 20-100 BoNT-B/Rima:500-2,000
	Rectus capitis lateralis	Tilt (ipsi)	-
	Posterior scalene	Tilt (ipsi) Mild rotation (contra)	BoNT-A/Ona/Inco: 5-30 BoNT-A/Abo: 20-100 BoNT-B/Rima: 500-2,000
POSTERIOR	Splenius capitis	Rotation (ipsi) Tilt (ipsi) Sagittal shift (backward) Extension (backward)	BoNT-A/Ona/Inco: 40-100 BoNT-A/Abo: 100-350 BoNT-B/Rima:1,000-4,000
	Semispinalis capitis	Rotation (contra)	BoNT-A/Ona/Inco: 20-100

		Tilt (ipsi) Extension (backward)	BoNT-A/Abo: 60-250 BoNT-B/Rima:1,000-2,000
	Trapezius	Shoulder elevation Extension (backward) Sagittal shift (backward) Tilt (ipsi) Rotation (assists in ipsi and contra)	BoNT-A/Ona/Inco: 25-100 BoNT-A/Abo: 60-300 BoNT-B/Rima:1,000-4,000
	Levator scapulae	Shoulder and scapula elevation Tilt (ipsi) Rotation (contra)	BoNT-A/Ona/Inco: 20-100 BoNT-A/Abo: 60-200 BoNT-B/Rima:1,000-2,000
	Obliquus capitis inferior	Rotation (ipsi)	BoNT-A/Ona/Inco: 10-20 BoNT-A/Abo: 50-80
	Rectus capitis posterior	Rotation (ipsi)	BoNT-A/Ona/Inco: 2,5-10 BoNT-A/Abo: 10-30

Antinociceptive effects of BoNT

Currently there is a lack of studies targeted pain assessment in CD for two main reasons. Firstly, there were formerly widely accepted direct association between pain relief and the muscle release as an effect of BoNT injection. However, it has been proven BoNT injection results in pain relief before muscle relaxation and this effect lasts longer than motor improvement. Moreover, the dose level of BoNT do not simply correlate with muscle relaxation. Secondly, scales used to the evaluation of CD symptoms in the past such as Tsui score were not targeted at pain specifically [19].

Above findings suggest that the analgesic effect of BoNT is attributed to the acting on central nervous system. Matak et al. reported that the peripheral BoNT injection resulted in the detection of enzymatic activity of BoNT in motor and sensory regions of the brainstem and spinal cord. BoNT/A activity in sensory regions was associated with its antinociceptive effects, however, the activity observed in motor regions remained unknown [20]. It has been also proven that BoNT attenuates peripheral sensitization as a result of the inhibition of the neurogenic inflammation by the attenuation of neurotransmitter release (glutamate, SP and CGRP) [21].

Clinical studies

The efficacy of BoNT was assessed in lots of clinical studies. A study enrolled 1,037 subjects with CD was the largest to date observational, multicenter and prospective investigation. Patients from CD PROBE (Cervical Dystonia Patient Registry for Observation of OnabotulinumtoxinA Efficacy) were divided into two groups with different level of pain:

mild or no pain (PNRS score 0-3) and moderate/severe pain (PNRS score 4-10). The moderate/severe level of pain correlated with the following factors:

- younger age,
- higher score in the severity subscale (17.7 ± 5.1 vs. 16.2 ± 5.6, $p < 0.0001$) and disability subscale (12.7 ± 6.1 vs. 7.5 ± 5.6, $p < 0.0001$) of TWSTRS,
- higher mean dose of ona-BoNT-A (177.3 ± 82.9 vs. 158.0 ± 67.1 U, $p = 0.0001$) and higher number of injected muscles (4.1 ± 1.4 vs. 3.7 ± 1.2, $p < 0.0001$) at initial treatment [22].

In another study of the improvement of quality of life and pain in 516 CD patients, BoNT injections resulted in pain relief (less or no pain) in 66% and 74.1% of patients at weeks 4 and 12 with the improvements in the scales of the quality of live [23].

Adverse events of BoNT

The data from seven clinical trials indicated that dysphagia and diffuse weakness or tiredness are the most common treatment-related adverse events (AEs). However, most of studies reported AEs after a single injection and data from RCTs evaluating the effectiveness and safety of repeated injection are lacking [2].

Dysphagia is usually mild, disappears after several weeks and is less frequent after ona-BoNT-A injections (3.4%) compared to inco-BoNT (12,6%), rima-BoNT (15,6%) and abo-BoNT (19,6%). The higher incidence of dysphagia may be also correlated with the injections into sternocleidomastoid and the anterior neck muscles with higher doses of neurotoxins [24].

Interestingly, the placebo effect may be responsible for a large proportion of AEs. The most recently published meta-analysis of 15 RCTs enrolling 1604 patients revealed even 79% of risk of overall AEs cannot be pharmacologically assigned to BoNT-A or BoNT-B injections. The detailed proportions of non-pharmacological symptoms accounts for up to 67% of weakness (BoNT-A only), 26% of dry mouth and 21% of dysphagia. Moreover, no statistically significant difference between BoNT and placebo characterized the frequency of following symptoms: injection site pain, headache, flu-like syndrome and dry mouth (BoNT-A only). On the other hand, BoNT injections were characterized by higher risk of AEs if the comparison referred to following reported events: dry mouth (RR, risk ratio, 7,12, BoNT-B only), dysphagia (RR 3,68), dry mouth (RR 3,00, overall) and weakness (1,78, BoNT-A only). Authors concluded that the only reported specific adverse events of BoNT administration were: weakness, dry mouth, and dysphagia. The distinguish between AEs

caused by BoNT and which come from patients' expectations poses a challenge to clinicians [25].

METHODS OF THE PAIN MANAGEMENT OPTIMIZATION

Poor response to BoNT

The rate of patients who discontinue therapy due to treatment failure, adverse effects, and other reasons accounts for even up to 20%. Generally, most poor responses are related to suboptimal treatment and a minority to immunoresistance which currently concerns only 0-2,5% of CD cases. The reduction in albumin content over the years from 25 ng to 5 ng probably contributes the declining frequency of BoNT-resistance. A disease progression may be a reason for secondary non-response assessed after two consecutive injections cycles [26,27].

The British Neurotoxin Network published the recommendations for the management of patients with a poor response to BoNT (Figure 1). In case of immunoresistance to BoNT-A, there are three other therapeutic options: the use use of BoNT-B or alternative BoNT-A, BoNT-A holidays or deep brain stimulation. Patients without immunoresistance may benefit from reviewing injections technique with electromyography or ultrasound guidance, different muscles selection or different dose of BoNT injections [26].

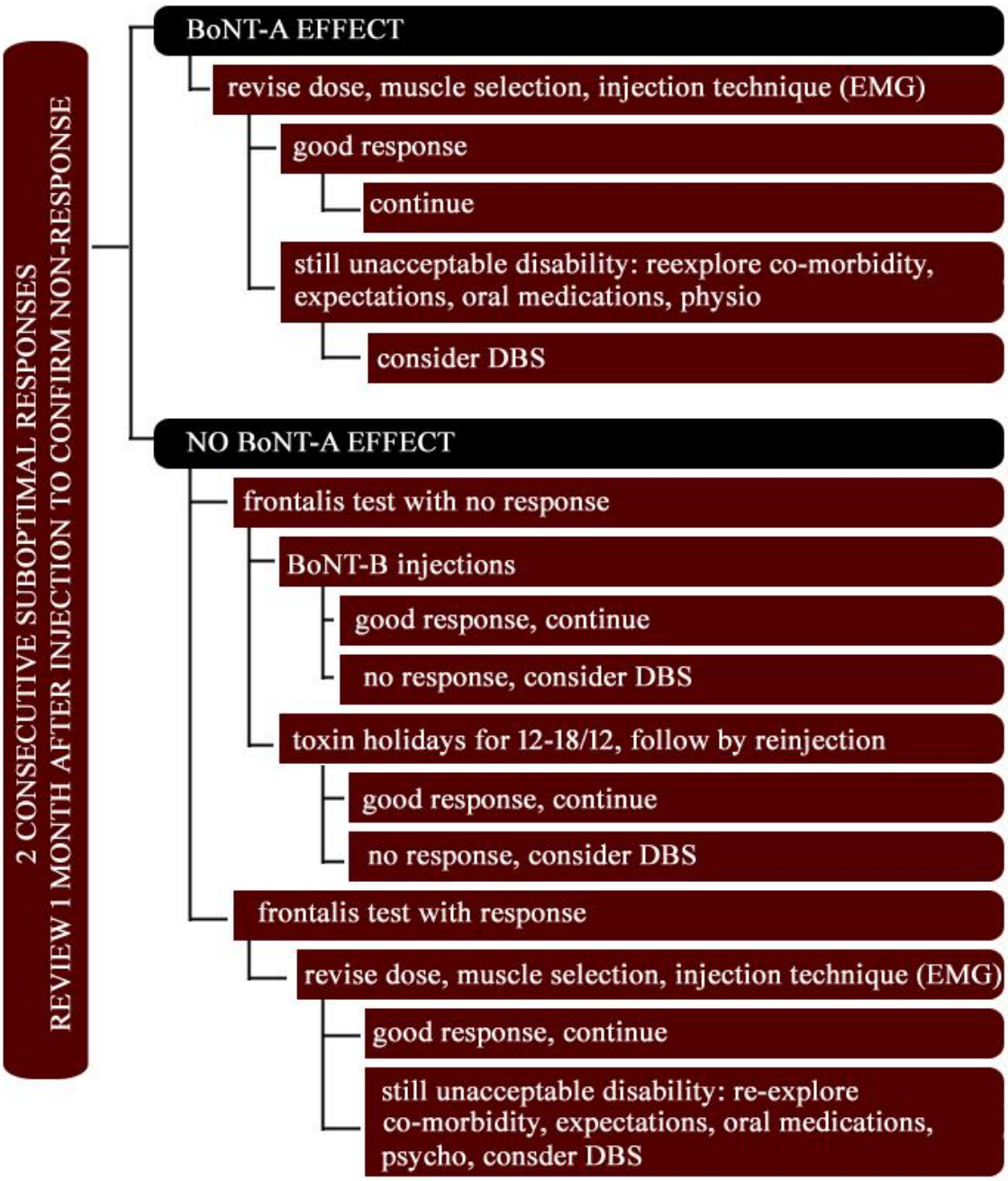

Figure 1. The recommendations of British Neurotoxin Network for managing CD in patients with a poor response to botulinum toxin. **BoNT** – botulinum toxin, **DBS** – deep brain stimulation, **EMG** – electromyography. **Frontalis test** is used to early diagnosis of immunoresistance. BoNT injections are given to the forehead 3 cm above the lateral and medial canthus of one eye. An asymmetric response after 2-4 weeks indicates that botulinum toxin has been effective. In case of an equivocal response higher dose of BoNT should be used or different test should be performed [26].

Ultrasonography and electromyography

One of the most important reasons for poor treatment outcomes and some side effects is the inappropriate identification of injection site. The palpation and analysis of head posture are the most commonly used methods, however, ultrasonography (US) and electromyography (EMG) may be useful in identifying dystonic muscles for BoNT treatment. A high capability in muscles illustrating provide the use of US in clinical practice [28]. There are several benefits of US application for the CD patients: non-invasive and quick muscle selection, a possibility of BoNT dose reduction and a chance for decreasing of the total number of injections. All above benefits may potentially ensure long-term efficacy of BoNT treatment [29]. US is accepted and recommended method supporting appropriate CD treatment [30].

Several studies evaluated the use of EMG during BoNT injections. A proper treatment of CD require to distinguish dystonic muscles from healthy muscles acting in compensation. Despite the fact that patients are always asked not to resist their dystonic posture, it is still unclear whether increased muscle activity in EMG results from the dystonic activity or compensatory muscle activation. The dystonic muscle activity was found during submaximal, but not maximal voluntary contractions and did not increase with an muscle contraction increase [31]. Furthermore, there is lack evidence that pain relief may be a result of the use of EMG. In one recently published study no significant difference was observed in VAS scores between EMG and palpation-guided BoNT injections. Benefits of EMG application included the lower incidence of dysphagia and prolonged benefit effects in Tsui scale. However, the invasiveness of this method resulted in higher incidence of discomfort and pain at the injection site [32].

R**ehabilitation**

Physiotherapy (PT) is a potentially useful adjuvant that may include muscular elongation, postural exercises and electrotherapy. Improvements in pain, head position, cervical range of motion, quality of life and activities of daily living are the major benefits from the PT. However, the low methodological quality of most studies and the lack of PT standardization in CD treatment complicates the physical therapists care management [33,34].

An integrated approach to idiopathic CD was presented in a study in which participants were divided into two treatment groups: the first received BoNT-A in combination with specific program of PT, the second received BoNT-A alone. A longer duration of the clinical improvement (118.8 vs. 99.1 days), a lower effective reinjection dose

of BoNT (284.5 vs. 325.5 units) and a greater reduction in subjective pain scores (-13.35 vs. -6.95 points) were reported in the group received BoNT combined with PT [35]. Similar results were reported in another study on PT program for CD management in which the significant improvements on the pain and disability subscales were seen in the group of patients receiving BoNT with PT [36].

Relaxation therapy

In contrast with most physical therapy interventions, a relaxation therapy is a recently proposed element of holistic perspective in CD beyond the dystonic focus. The pilot study in 2018 assessed changes in pain scales (VAS and TWSTRS) due to the relaxation therapy in CD treatment. Patients received 4 individual sessions of an Watsu aquatic therapy (one per week) and an autogenic training at home twice a day (for over 1 month) were compared to the control group. A significant pain decrease was observed. The authors concluded that an intervention that addresses physical and mental stressors improved the symptoms of patients with CD [33].

Oral medications

There is a lack of randomized controlled trials on the treatment of CD-related pain with use of oral drugs and only a few non-controlled studies or clinical reports. Trihexyphenidyl, an anticholinergic, was the most widely accepted treatment for CD prior to the introduction of BTA. Currently, despite confirmed effectiveness in CD treatment, the anticholinergics are not routinely used in CD treatment due to more objective and subjective benefits of BoNT injections with less adverse events [37,38]. It should be noticed that such oral medications as opiates and benzodiazepines increase the risk of the development of the substance abuse, which may be observed in almost 11% of patients with CD [39].

Intrathecal baclofen

A significant pain reduction, as well as spasticity in cervical and other focal dystonias, was found to be an effect of intrathecal baclofen administration. However, the procedure is uncommon (there is only a few cases report published) and technically challenging. The possible complications (cerebrospinal fluid leakage, wound dehiscence, catheter disconnection or dislodgment, meningitis) contribute to decrease the cost-benefit ratio of intervention. Above procedure, if applied at high level of cervical spine (C1-3), may be used in medically refractory CD [40,41].

Deep brain stimulation

Deep brain stimulation (DBS) of the globus pallidus is the most recommended surgery procedure in CD treatment and is usually considered when medication or BoNT have failed [42,43]. Several clinical trials on DBS treatment in CD were performed, however most of them enrolled only a small number of participants. Generally, improvement in pain subscale of TWSTRS are high with the range from 66.8% up to 92% improvement compared to baseline score [44,45].

A specialized expertise and a multidisciplinary team are necessary to perform this procedure. Due to several side effects DBS can be applied only if the risk-benefit balance remains favourable [15]. However, there are some patients who might prefer a one long-latsing approach (DBS) to repeated botulinum toxin treatment. Before giving a recommendation to a patient about DBS as a treatment option, all reasons for clinical non-response should be considered (inappropriate injection schemes, insufficient dosing, wrong muscle selection, an insufficient number of treatment attempts) [43].

Transcranial direct or alternating current stimulation

There are two methods of non-invasive stimulation of the cerebellum and primary motor cortex: transcranial direct current stimulation (tDCS) in which anodal pole stimulates and cathodal pole inhibits the underlying cortex, and transcranial alternating current stimulation (tACS) in which both poles have equivalent frequency-dependent effects on the underlying cortex. A few consecutive daily sessions of tDCS or tACS are administered to the patient by the selected sponge electrodes from the international 10/20 EEG electrode system. One of the first reports of one CD patient treated with tACS demonstrated significant therapeutic effect: up to 75% reduction in the pain subscale and up to 54% in the total TWSTRS [46]. In another case report, a 12 week period of tDCS application in combination with usual treatment of BoNT revealed following score reductions: 55% in the TWSTRS pain subscale, 40% in the CDQ-24 and 39% in the CDIP-58. The augmentation of BoNT injection seems to be a major effect of tDCS [47]. Despite the possible effectiveness of tDCS and tACS, clinical trials are still lacking.

CONCLUSIONS

Pain in the course of CD is common and disabling symptom which strongly deteriorates the quality of life. BoNT administration is recommended as a first line treatment

with documented effectiveness, however, not all patients benefits from this therapy for several reasons. The currently available managements of improving the efficacy of first-line treatment include: the eradication of BoNT adverse events, the determination of individual BoNT dosage, the proper identification of the injection sites by the use of additional techniques (US, EMG), the implementation of a rehabilitation program and the applying of the invasive (DBS) or non-invasive (tDCS or tACS) brain stimulation methods. Further studies are needed to issue an unambiguous recommendations of the use of above methods in the CD-related pain.

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