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**Author(s)**

Contarino, Maria Fiorella; Smit, Marenka; van den Dool, Joost; Volkmann, Jens; Tijssen, Marina A.J.

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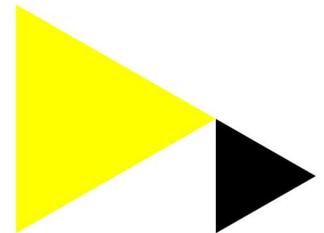
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# Unmet Needs in the Management of Cervical Dystonia

**Maria Fiorella Contarino<sup>1,2</sup>, Marenka Smit<sup>3</sup>, Joost van den Dool<sup>3,4,5</sup>, Jens Volkmann<sup>6†</sup> and Marina A. J. Tijssen<sup>3\*†</sup>**

<sup>1</sup>Department of Neurology, Leiden University Medical Centre, Leiden, Netherlands, <sup>2</sup>Department of Neurology, Haga Teaching Hospital, The Hague, Netherlands, <sup>3</sup>Department of Neurology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, <sup>4</sup>Faculty of Health, ACHIEVE Centre of Applied Research, Amsterdam University of Applied Sciences, Amsterdam, Netherlands, <sup>5</sup>Department of Neurology, Academic Medical Center, Amsterdam, Netherlands, <sup>6</sup>Department of Neurology, University Clinic of Würzburg, Würzburg, Germany

Cervical dystonia (CD) is a movement disorder which affects daily living of many patients. In clinical practice, several unmet treatment needs remain open. This article focuses on the four main aspects of treatment. We describe existing and emerging treatment approaches for CD, including botulinum toxin injections, surgical therapy, management of non-motor symptoms, and rehabilitation strategies. The unsolved issues regarding each of these treatments are identified and discussed, and possible future approaches and research lines are proposed.

**Keywords:** cervical dystonia, botulinum toxin, deep brain stimulation, physical therapy modalities, non-motor features

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### \*Correspondence:

Marina A. J. Tijssen  
m.a.j.de.koning-tijssen@umcg.nl

<sup>†</sup>Jens Volkmann and Marina A. J.  
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## INTRODUCTION

Cervical dystonia (CD) is the most prevalent form of adult-onset focal dystonia, and is characterized by abnormal postures of head and neck, that can considerably impair daily living.

There are several unmet needs in the management of CD. In this article, we focused on four main aspects of the treatment of this disorder, including botulinum toxin injections, surgical therapy, management of non-motor symptoms (NMS), and rehabilitation strategies.

For each of these issues the state-of-the art is presented and some of the current knowledge gaps are highlighted. In addition, we propose potential research lines that could be developed to manage these issues.

## BOTULINUM TOXIN

### What Is Known?

Botulinum neurotoxin (BoNT) injections are the treatment of choice for CD.

There is class I evidence to support efficacy and safety of the three commercially available formulations of BoNT-A (onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA) (1–3), and of BoNT-B (rimabotulinumtoxin B) (4).

As much as 70–85% of the patients report a significant benefit from the treatment (5). Efficacy on motor symptoms varies from 20 to 70%, based on the assessing method used. Significant improvement is also documented on pain and quality of life (QoL) (6).

Although BoNT treatment is routinely performed worldwide and is satisfying for many patients, the obtained effect is still far from optimal. In addition, BoNT treatment is in some cases associated with the occurrence of side effects, such as dysphagia or excessive muscle weakness. These side effects

are due to an excessive dose of BoNT or to the spread of BoNT to adjacent structures, and may limit the efficacy of the treatment.

## What Is Uncertain?

In order to further improve the efficacy and safety of the treatment, the accurate placement of the minimum effective dose of toxin in the dystonic muscles should be ensured. At present, there is still no agreement on a recommended starting dose or on the minimum effective dose per muscle.

Moreover, there is still great variability concerning treatment strategies. Multi-point BoNT injections have been proposed as more effective than single point injections (7), but convincing evidence on these topics is still lacking.

The use of polymyography to identify dystonic muscles before treatment, and the use of electromyography (EMG) to guide injections, has been proposed to improve the accuracy of BoNT delivery. While some studies show that this approach may provide a significant advantage in BoNT-naïve patients (8, 9), as well as in patients unsatisfactorily treated with standard injections (10, 11), this still need to be further confirmed in larger series. Moreover, the modalities and indications of the neurophysiological approach need to be further specified.

The use of imaging techniques has also been proposed to identify the dystonic muscles before treatment and to improve the accuracy of the placement of BoNT. Preliminary reports suggest that the use of ultrasound-guided injections might help localizing the target muscles and reducing the episodes of dysphagia in patients who had experienced it with standard treatment (12).

A number of patients do not respond to BoNT treatment, or develop a secondary resistance. A currently accepted definition of secondary non-responsiveness implies “insufficiently improved posture after three or more unsuccessful injection cycles in CD patient’s previously achieving satisfactory results” (13).

Change in CD pattern across time, with the appearance of more complex multiaxial dystonic movements or tremor, account for some of the non-responders. Another well-known cause of non-responsiveness is the development of antibodies against BoNT formulations (14). This issue has been described with different BoNT formulations, including onabotulinumtoxinA, abobotulinumtoxinA, and rimabotulinumtoxinB (15), while it does not seem to be a concern when incobotulinumtoxinA is used (16). At present, there is no agreement on the strategies to avoid the formation of antibodies. Although this problem likely occurs only sporadically, a minimum safe interval of 12 weeks or longer is still used in most centers (17). This strategy, however, limits treatment of a larger number of patients, who report reemergence of symptoms before this time. The safety of shorter intervals between injections and of the so-called booster injections still needs to be explored.

Another unsolved and largely debated practical issue concerns the optimal conversion ratio between different formulation of BoNT-A, or between BoNT-A and BoNT-B.

Based on studies using different methodology, a conversion of onabotulinumtoxinA to abobotulinumtoxinA 1:3 IU (18, 19), as well as ratios of 1:2.5 (20) have been proposed over time, while a conversion ratio of 1:1 is proposed for onabotulinumtoxinA to incobotulinumtoxinA.

## Future Perspectives

Future research lines should focus on improving the benefit/side effects ratio of BoNT treatment and on reducing the rate of primary and secondary non-responsive patients.

A standardized working definition of non-responsiveness should be developed, which should take into account an objective measure of the lack of improvement as well as an evaluation of the appropriateness of BoNT treatment. An objective and universally accepted working definition would be of crucial importance to assess new treatment strategies and to identify patients for whom more invasive (surgical) treatment are indicated.

Dose-finding studies and comparative studies across different toxins should be performed. The additional value of neurophysiology and imaging in improving the intramuscular placing of BoNT should be explored. In order to minimize patients’ discomfort, the minimum safe interval between treatments should be determined.

## SURGICAL TREATMENT

### What Is Known?

Deep brain stimulation (DBS) of the internal globus pallidus (GPi) is an established surgical treatment for patients with generalized dystonia (21, 22). Because the initial studies suggested an equally beneficial effect for all body regions, the method was soon applied to patients with focal or segmental dystonias, who no longer responded to BoNT.

Krauss was the first to describe the beneficial outcome in three patients with CD in 1999 (23). Meanwhile three controlled clinical studies were conducted evaluating GPi-DBS in CD patients who failed on medical treatment: a Canadian prospective, multicenter and observer-blinded study assessed 10 CD patients who were further followed for 12 months (24). Motor improvement was 28% at 6 months and 43% at 12 months (TWSTRS motor score). Pain and disability scores were also improved by 66 and 64%, as well as mood [Beck’s Depression Inventory (BDI)] and QoL (SF-36) by 58 and 24%, respectively. Another prospective single-center study followed eight CD patients for up to 48 months after GPi-DBS (25), reporting a median reduction in the TWSTRS motor score of 50% at 6 months and of 73% at last follow-up. The only randomized sham-controlled multicenter study of bilateral GPi-DBS in CD followed patients for a total of 6–9 months after surgery (26). Sixty-two patients were implanted with a neurostimulation system and randomly assigned to either active or sham stimulation (stimulator output 0V). After 3 months, TWSTRS severity score was reduced by 26% in the treatment group compared to 6% in the sham group. There was a 3.8 point difference between both groups, which was significant. TWSTRS disability score and Bain tremor score were also significantly improved in the neurostimulation group, whereas TWSTRS pain score and QoL (Cranio-cervical Dystonia Questionnaire-24 score) were not different. Evaluations were repeated in all patients after receiving 6 months of effective neurostimulation. At the follow-up, significant improvements compared to the pre-surgical baseline were found for TWSTRS severity score (28%), disability score (46%) and pain (51%),

Tsui score (57%), Bain tremor score (66%), and global dystonia ratings by patients (49%) or physicians (53%). BDI was reduced by 20%, the cranio-cervical dystonia questionnaire-24 showed a 28% improvement. No permanent adverse effects were found. Transient adverse effects included device infection ( $n = 3$ ), misplacement/dislocation of electrodes ( $n = 3$ ) or neurostimulator ( $n = 1$ ), stroke/hemorrhage ( $n = 1$ ), and seizure ( $n = 1$ ). Four patients claimed pain at the extension cable. The most frequent stimulation-induced side-effect was dysarthria (seven patients). Stimulation-induced bradykinesia was observed in one patient, but has previously been described as a relevant adverse effect of pallidal neurostimulation in several series (27, 28).

It has been suggested that the subthalamic nucleus could be a better target for DBS in CD with equal motor benefit but less risk of stimulation-induced parkinsonism (29).

## What Is Uncertain?

Larger series are needed to ascertain which types of CD respond best to pallidal DBS, and to assess predisposing factors and the true prevalence and risk factors of stimulation-induced parkinsonism. Subthalamic stimulation, which was forwarded as an alternative, induces (transient) dyskinesia in a large proportion of patients and the cognitive and behavioral safety has not been evaluated yet. So far, DBS has been advocated only in patients no longer responding to BoNT treatment, as a last line therapy. A comparative trial of BoNT treatment in comparison to DBS has not been performed yet.

## Future Perspectives

Registry data of DBS surgery in CD would help to evaluate outcomes in daily practice, define responder profiles, and assess the frequency of less common adverse effects. The effect of DBS on non-motor features should be systematically assessed. Randomized controlled trials (RCTs) are needed to compare pallidal and subthalamic neurostimulation and DBS in general vs. best conservative management of CD.

## MANAGEMENT OF NON-MOTOR SYMPTOMS

### What Is Known?

Growing evidence suggests that the phenotype of dystonia includes also NMS, which could in part account for the reduced QoL in CD (30, 31).

Sensory abnormalities are the most frequently NMS associated with CD. The onset of motor symptoms can be preceded by a feeling of discomfort in the neck and dystonic movements are sometimes interpreted as an attempt to decrease this feeling (32). Involvement of the sensory system is also indicated by the *geste antagoniste*, which modifies cortical EEG activity and GPI local field potentials, even before touching the head (33). Furthermore, several studies found abnormalities in temporal and spatial discrimination thresholds in CD patients, both in affected and unaffected body parts, and in unaffected first-degree relatives (34, 35).

Pain is present in up to 90% of CD patients, which is rated as moderate to severe by 70% (36). Two-third of the patients use analgesics. Pain might be a consequence of motor symptom severity (37), but could also be influenced by depressive and anxiety symptoms (31). It is proven that BoNT treatment as well as surgical treatments, such as DBS (26) or selective peripheral denervation (38), significantly improves pain associated with CD (36, 37).

The prevalence of psychiatric disorders in CD can reach up to 91.4%, compared to 35% in the general population (39). This could logically be the consequence of living with a chronic, visible, and invalidating disorder. However, compared to the prevalence of psychiatric symptoms in other chronic and visible diseases, such as alopecia areata, CD patients still have a significantly increased odds ratio to develop psychiatric co-morbidity (40). The most prevalent psychiatric disorders include depressive symptoms (40–45), anxiety symptoms/panic disorders (39, 40, 44, 45), obsessive-compulsive symptoms (41, 45) and substance abuse (45). Importantly, a few studies showed that psychiatric co-morbidity is the most important predictor of poorer health-related QoL, especially for the domains general health, role functioning, bodily pain, and emotional and mental health (31, 46, 47).

At this moment, no treatment trials have been described with the aim to directly improve psychiatric symptoms in CD patients.

### What Is Uncertain?

The prevalence and characteristics of the different NMS in CD, including sleep disturbances and cognition, have not been systematically studied and existing studies show contrasting results. A recurring debate is whether NMS are a direct consequence of the motor symptoms of dystonia or intrinsic to the neurobiology and thereby part of the phenotype.

Cervical dystonia patients showed an impaired sleep quality compared to healthy controls: in two studies, this was correlated with depressive symptom scores (48, 49), while in one study it appeared to be independent from psychiatric disorders and medication use (50). Successful BoNT treatment did not improve sleep quality, arguing against a secondary discomfort due to the dystonia motor symptoms (50). Excessive daytime sleepiness was detected in one study, but at least in part explained by the use of anticholinergic drugs (51). Other studies did not find significant differences in daytime sleepiness (48, 49).

Studies concerning cognitive impairment in CD are still very limited. One study showed impairments in the domains working memory, processing speed, visual motor ability, and short-term memory (52). Other small studies found impairment of visuospatial function (53) and a sustained attention deficit, the latter disappearing after BoNT treatment (54).

Convincing data support a disruption of sensory-motor system also in healthy first-degree relatives of dystonic patients, suggesting a possible endophenotype (55). For example, temporal discrimination threshold (TDT) was found abnormal not only in about 80% of dystonia patients but also in about 50% of first-degree female relatives older than 48. In male relatives, the penetrance was reduced (34, 56).

The onset of psychiatric disorders before the onset of the movement disorder in ~70% of the cases (42, 44, 45) is one of

the strongest arguments toward a shared pathophysiology. This is also supported by a men-to-women ratio of psychiatric disorders of 1:1 in CD patients compared to 1:2 in the general population, higher incidence of psychiatric disorders in CD patients compared to other visible and chronic disorders, and different personality profiles found in CD patients, which develop long before adolescence and onset of motor symptoms (35).

Drawing firm conclusions on the etiology of NMS in CD remains difficult, also considering the tight correlation between pain, psychiatric symptoms, sleep disturbances, and motor symptoms.

## Future Perspectives

In order to solve the issue of the etiology of NMS in CD, prospective studies are necessary. Selecting an appropriate group for prospective studies has proven challenging. This might change with the identification of genetic forms of CD, such as the *GNAL* and *ANO3* gene (57–60), which would allow studying homogeneous clinical subgroups, even in the pre-symptomatic phase.

Another strategy could be the identification of endophenotypes in larger groups, based on biomarker, such as the TDT.

Clinical trials are required toward the effect of treatment of NMS on health-related QoL.

## REHABILITATION STRATEGIES

### What Is Known?

Evidence toward the effectiveness of rehabilitation strategies is scarce. Two systematic reviews described the effects of different rehabilitation strategies in various forms of primary dystonia (61) and CD alone (62), suggesting that multimodal physical therapy (PT) programs, added to BoNT treatment, further improve disability and pain compared to BoNT treatment alone (61, 62). Only three clinical trials (63–65) and one case–control study (66) investigated the effects of a multimodal PT program in combination with BoNT treatment.

One single-blind RCT in 40 patients showed significant improvements on pain and daily-life activities, and a prolonged duration of the BoNT effect, after a 6-week PT program of active exercises, muscle stretching and massage compared to BoNT treatment alone (63). A second single-blind RCT in 40 patients showed decreased disability and a significant decrease of head deviation and improved hand functions after a 6-week PT program of active exercise, muscle stretching, and TENS in addition to BoNT treatment (64). The third single-blind RCT of 20 patients found only a trend toward greater improvement on head posture, pain, and disability in the group that received 12 weeks of active exercise, relaxation, and BoNT treatment compared to the group that received relaxation and BoNT treatment only (65).

One case–control study followed 40 patients in a 4-week PT program of active exercise, muscle stretching, active and passive neck mobilizations, and electrostimulation of the dystonic muscles in adjunction to BoNT treatment, or BoNT treatment alone. The PT group showed significantly more improvement on pain, and on some subscales of the SF-36 (66).

### What Is Uncertain?

The available results should be interpreted with caution. The content of PT programs varied across studies, including motor learning exercises [Bleton method (67)], passive or active mobilization techniques of the cervical spine, stretching of the dystonic muscles, relaxation, and electrotherapy, such as EMG biofeedback or TENS. It is, therefore, difficult to identify the most effective intervention or combination of interventions.

Frequency and duration of PT sessions also varied from 40 min every other day for 6 weeks (64), 75 min 5 days a week for 5 weeks (66), 90 min a day for 2 weeks (63) up to a 12-week program with a weekly 30-min session during the first 4-weeks, and a session every fortnight for the remaining 8 weeks (65). Besides, current studies mainly show short-term effects associated with brief and intensive PT programs (63, 64, 66), which could be difficult to implement in current regular care of a chronic disease, such as CD. The long-term effects of less intense and longer PT programs have not been explored yet.

### Future Perspectives

Future research should focus on standardized PT programs that are effective but also adequate to treat patients with a chronic conditions and an active life. PT programs with longer treatment periods and the emphasis on self-management of symptoms and the ability of patients to improve their performance of daily life tasks should be the focus. Currently, such a PT program is being investigated in a large Dutch RCT (68).

The effect of PT interventions on the pathophysiological mechanisms of CD should also be studied. Although the pathophysiology of CD remains largely unclear, maladaptive neuroplastic changes may play an important role (69). By integrating PT programs with modern training principles that have proven relevant for neural rehabilitation and motor learning, these deficit may be altered (70–74).

Additionally, high-quality research combining electrophysiological parameters or imaging techniques with clinical outcomes can help to further unravel the effects of PT programs on CD.

## FINAL CONSIDERATIONS

There are still many unmet needs in the management of CD. A better understanding of the pathophysiology of CD is necessary to plan new treatment strategies and to improve existing treatments. In addition, the available rating scales for CD have some clinimetric issues and do not equally address all the domains of the disease. This points to a need for updated scoring instruments in order to support studies on the pathogenesis and progression of the disease and to more accurately evaluate the outcomes of clinical trials. Specific standardized rating scale for NMS in (cervical) dystonia should also be developed.

Finally, it is widely accepted that motor improvement is not the only determinant of treatment success in CD: pain, social distress, and psychological factors play sometimes a greater role toward patient satisfaction. This calls for a multi-disciplinary approach posing more attention to the subjective determinants of QoL in CD.

## AUTHOR CONTRIBUTIONS

All the authors (MC, MS, JD, JV, and MT) provided substantial contributions to the conception or design of the work; drafted

part of the manuscript and revised the rest of the manuscript critically for important intellectual content; approved the final version to be published; agreed to be accountable for all aspects of the work.

## REFERENCES

- Poewe W, Deuschl G, Nebe A, Feifel E, Wissel J, Benecke R, et al. What is the optimal dose of botulinum toxin A in the treatment of cervical dystonia? Results of a double blind, placebo controlled, dose ranging study using Dysport. German Dystonia Study Group. *J Neurol Neurosurg Psychiatry* (1998) 64:13–7. doi:10.1136/jnnp.64.1.13
- Charles D, Brashear A, Hauser RA, Li HI, Boo LM, Brin MF, et al. Efficacy, tolerability, and immunogenicity of onabotulinumtoxinA in a randomized, double-blind, placebo-controlled trial for cervical dystonia. *Clin Neuropharmacol* (2012) 35:208–14. doi:10.1097/WNF.0b013e31826538c7
- Comella CL, Jankovic J, Truong DD, Hanschmann A, Grafe S, U.S. XEOMIN Cervical Dystonia Study Group. Efficacy and safety of incobotulinumtoxinA (NT 201, XEOMIN(R), botulinum neurotoxin type A, without accessory proteins) in patients with cervical dystonia. *J Neurol Sci* (2011) 308:103–9. doi:10.1016/j.jns.2011.05.041
- Brashear A, Lew MF, Dykstra DD, Comella CL, Factor SA, Rodnitzky RL, et al. Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-responsive cervical dystonia. *Neurology* (1999) 53:1439–46. doi:10.1212/WNL.53.7.1439
- Truong D, Duane DD, Jankovic J, Singer C, Seeburger LC, Comella CL, et al. Efficacy and safety of botulinum type A toxin (Dysport) in cervical dystonia: results of the first US randomized, double-blind, placebo-controlled study. *Mov Disord* (2005) 20:783–91. doi:10.1002/mds.20403
- Mordin M, Masaquel C, Abbott C, Copley-Merriman C. Factors affecting the health-related quality of life of patients with cervical dystonia and impact of treatment with abobotulinumtoxinA (Dysport): results from a randomized, double-blind, placebo-controlled study. *BMJ Open* (2014) 4:e005150. doi:10.1136/bmjopen-2014-005150
- Borodic GE, Pearce LB, Smith K, Joseph M. Botulinum a toxin for spasmodic torticollis: multiple vs single injection points per muscle. *Head Neck* (1992) 14:33–7. doi:10.1002/hed.2880140108
- Werdelin L, Dalager T, Fuglsang-Frederiksen A, Regeur L, Karlsborg M, Korbo L, et al. The utility of EMG interference pattern analysis in botulinum toxin treatment of torticollis: a randomised, controlled and blinded study. *Neurophysiol Clin* (2011) 122:2305–9. doi:10.1016/j.clinph.2011.04.012
- Comella CL, Buchman AS, Tanner CM, Browntoms NC, Goetz CG. Botulinum toxin injection for spasmodic torticollis – increased magnitude of benefit with electromyographic assistance. *Neurology* (1992) 42:878–82. doi:10.1212/WNL.42.4.878
- Nijmeijer SWR, Koelman JHTM, Standaar TSM, Postma M, Tijssen MAJ. Cervical dystonia: improved treatment response to botulinum toxin after referral to a tertiary centre and the use of polymyography. *Parkinsonism Relat Disord* (2013) 19:533–8. doi:10.1016/j.parkreldis.2013.01.018
- Cordivari C, Misra VP, Vincent A, Catania S, Bhatia KP, Lees AJ. Secondary nonresponsiveness to botulinum toxin a in cervical dystonia: the role of electromyogram-guided injections, botulinum toxin a antibody assay, and the extensor digitorum brevis test. *Mov Disord* (2006) 21:1737–41. doi:10.1002/mds.21051
- Hong JS, Sathe GG, Niyonkuru C, Munin MC. Elimination of dysphagia using ultrasound guidance for botulinum toxin injections in cervical dystonia. *Muscle Nerve* (2012) 46:535–9. doi:10.1002/mus.23409
- Ferreira JJ, Colosimo C, Bhidayasiri R, Marti MJ, Maisonobe P, Om S. Factors influencing secondary non-response to botulinum toxin type A injections in cervical dystonia. *Parkinsonism Relat Disord* (2015) 21:111–5. doi:10.1016/j.parkreldis.2014.09.034
- Greene P, Fahn S, Diamond B. Development of resistance to botulinum toxin type A in patients with torticollis. *Mov Disord* (1994) 9:213–7. doi:10.1002/mds.870090216
- Kessler KR, Skutta M, Benecke R. Long-term treatment of cervical dystonia with botulinum toxin A: efficacy, safety, and antibody frequency. German Dystonia Study Group. *J Neurol* (1999) 246:265–74.
- Dressler D, Tacik P, Adib Saberi F. Botulinum toxin therapy of cervical dystonia: comparing onabotulinumtoxinA (Botox((R))) and incobotulinumtoxinA (Xeomin ((R))). *J Neural Transm (Vienna)* (2014) 121:29–31. doi:10.1007/s00702-013-1076-z
- Novak I, Campbell L, Boyce M, Fung VS, Cerebral Palsy Institute. Botulinum toxin assessment, intervention and aftercare for cervical dystonia and other causes of hypertonia of the neck: international consensus statement. *Eur J Neurol* (2010) 17(Suppl 2):94–108. doi:10.1111/j.1468-1331.2010.03130.x
- Odergren T, Hjalton H, Kaakkola S, Solders G, Hanko J, Fehling C, et al. A double blind, randomised, parallel group study to investigate the dose equivalence of Dysport and Botox in the treatment of cervical dystonia. *J Neurol Neurosurg Psychiatry* (1998) 64:6–12. doi:10.1136/jnnp.64.1.6
- Ranoux D, Gury C, Fondarai J, Mas JL, Zuber M. Respective potencies of Botox and Dysport: a double blind, randomised, crossover study in cervical dystonia. *J Neurol Neurosurg Psychiatry* (2002) 72:459–62.
- Yun JY, Kim JW, Kim HT, Chung SJ, Kim JM, Cho JW, et al. Dysport and Botox at a ratio of 2.5:1 units in cervical dystonia: a double-blind, randomized study. *Mov Disord* (2015) 30:206–13. doi:10.1002/mds.26085
- Vidalhet M, Vercueil L, Houeto JL, Krystkowiak P, Benabid AL, Cornu P, et al. Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. *N. Engl. J. Med* (2005) 352:459–67. doi:10.1056/NEJMoa042187
- Kupsch A, Benecke R, Mueller J, Trottenberg T, Schneider G-H, Poewe W, et al. Pallidal deep-brain stimulation in primary generalized or segmental dystonia. *New Engl J Med* (2006) 355:1978–90. doi:10.1056/NEJMoa063618
- Krauss JK, Pohle T, Weber S, Ozdoba C, Burgunder JM. Bilateral stimulation of globus pallidus internus for treatment of cervical dystonia. *Lancet* (1999) 354:837–8. doi:10.1016/S0140-6736(99)03084-6
- Kiss ZHT, Doig-Beyaert K, Eliasziw M, Tsui J, Haffenden A, Suchowersky O, et al. The Canadian multicentre study of deep brain stimulation for cervical dystonia. *Brain* (2007) 130:2879–86. doi:10.1093/brain/awm229
- Skogseid IM, Ramm-Petersen J, Volkmann J, Kerty E, Dietrichs E, Roste GK. Good long-term efficacy of pallidal stimulation in cervical dystonia: a prospective, observer-blinded study. *Eur J Neurol* (2012) 19:610–5. doi:10.1111/j.1468-1331.2011.03591.x
- Volkmann J, Mueller J, Deuschl G, Kuhn AA, Krauss JK, Poewe W, et al. Pallidal neurostimulation in patients with medication-refractory cervical dystonia: a randomised, sham-controlled trial. *Lancet Neurol* (2014) 13:875–84. doi:10.1016/S1474-4422(14)70143-7
- Schrader C, Capelle HH, Kinfe TM, Blahak C, Bazner H, Lutjens G, et al. GPI-DBS may induce a hypokinetic gait disorder with freezing of gait in patients with dystonia. *Neurology* (2011) 77:483–8. doi:10.1212/WNL.0b013e318227b19e
- Berman BD, Starr PA, Marks WJ Jr, Ostrem JL. Induction of bradykinesia with pallidal deep brain stimulation in patients with cranial-cervical dystonia. *Stereotact Funct Neurosurg* (2009) 87:37–44. doi:10.1159/000195718
- Ostrem JL, Racine CA, Glass GA, Grace JK, Volz MM, Heath SL, et al. Subthalamic nucleus deep brain stimulation in primary cervical dystonia. *Neurology* (2011) 76:870–8. doi:10.1212/WNL.0b013e31820f2e4f
- Ben-Shlomo Y, Camfield L, Warner T, Grp EC. What are the determinants of quality of life in people with cervical dystonia? *J Neurol Neurosurg Psychiatry* (2002) 72:608–14. doi:10.1136/jnnp.72.5.608
- Pekmezovic T, Svetel M, Ivanovic N, Dragasevic N, Petrovic I, Tepavcevic DK, et al. Quality of life in patients with focal dystonia. *Clin Neurol Neurosurg* (2009) 111:161–4. doi:10.1016/j.clineuro.2008.09.023
- Stamelou M, Edwards MJ, Hallett M, Bhatia KP. The non-motor syndrome of primary dystonia: clinical and pathophysiological implications. *Brain* (2012) 135:1668–81. doi:10.1093/brain/awr224
- Tang JK, Mahant N, Cunic D, Chen R, Moro E, Lang AE, et al. Changes in cortical and pallidal oscillatory activity during the execution of a sensory trick

- in patients with cervical dystonia. *Exp Neurol* (2007) 204:845–8. doi:10.1016/j.expneurol.2007.01.010
34. Kimmich O, Molloy A, Whelan R, Williams L, Bradley D, Balsters J, et al. Temporal discrimination, a cervical dystonia endophenotype; penetrance and functional correlates. *Mov Disord* (2014) 29:804–11. doi:10.1002/mds.25822
  35. Zurowski M, McDonald WM, Fox S, Marsh L. Psychiatric comorbidities in dystonia: emerging concepts. *Mov Disord* (2013) 28:914–20. doi:10.1002/mds.25501
  36. Camargo CH, Cattai L, Teive HA. Pain relief in cervical dystonia with botulinum toxin treatment. *Toxins (Basel)* (2015) 7:2321–35. doi:10.3390/toxins7062321
  37. Charles PD, Adler CH, Stacy M, Comella C, Jankovic J, Manack Adams A, et al. Cervical dystonia and pain: characteristics and treatment patterns from CD PROBE (cervical dystonia patient registry for observation of onabotulinumtoxin A efficacy). *J Neurol* (2014) 261:1309–19. doi:10.1007/s00415-014-7343-6
  38. Bergenheim AT, Nordh E, Larsson E, Hariz MI. Selective peripheral denervation for cervical dystonia: long-term follow-up. *J Neurol Neurosurg Psychiatry* (2015) 86:1307–13. doi:10.1136/jnnp-2014-307959
  39. Gundel H, Wolf A, Xidara V, Busch R, Ceballos-Baumann AO. Social phobia in spasmodic torticollis. *J Neurol Neurosurg Psychiatry* (2001) 71:499–504. doi:10.1136/jnnp.71.4.499
  40. Gundel H, Wolf A, Xidara V, Busch R, Ladwig KH, Jacobi F, et al. High psychiatric comorbidity in spasmodic torticollis: a controlled study. *J Nerv Ment Dis* (2003) 191:465–73. doi:10.1097/01.NMD.0000081667.02656.21
  41. Bihari K, Hill JL, Murphy DL. Obsessive-compulsive characteristics in patients with idiopathic spasmodic torticollis. *Psychiatry Res* (1992) 42:267–72. doi:10.1016/0165-1781(92)90118-M
  42. Fabbrini G, Berardelli I, Moretti G, Pasquini M, Bloise M, Colosimo C, et al. Psychiatric disorders in adult-onset focal dystonia: a case-control study. *Mov Disord* (2010) 25:459–65. doi:10.1002/mds.22983
  43. Jahanshahi M, Marsden CD. Depression in torticollis: a controlled study. *Psychol Med* (1988) 18:925–33. doi:10.1017/S0033291700009855
  44. Moraru E, Schnider P, Wimmer A, Wenzel T, Birner P, Griengl H, et al. Relation between depression and anxiety in dystonic patients: implications for clinical management. *Depress Anxiety* (2002) 16:100–3. doi:10.1002/da.10039
  45. Wenzel T, Schnider P, Wimmer A, Steinhoff N, Moraru E, Auff E. Psychiatric comorbidity in patients with spasmodic torticollis. *J Psychosom Res* (1998) 44:687–90. doi:10.1016/S0022-3999(97)00229-8
  46. Ben-Shlomo Y, Camfield L, Warner T, ESDE Collaborative Group. What are the determinants of quality of life in people with cervical dystonia? *J Neurol Neurosurg Psychiatry* (2002) 72:608–14. doi:10.1136/jnnp.72.5.608
  47. Slawek J, Friedman A, Potulska A, Krystkowiak P, Gervais C, Banach M, et al. Factors affecting the health-related quality of life of patients with cervical dystonia and the impact of botulinum toxin type A injections. *Funct Neurol* (2007) 22:95–100.
  48. Avanzino L, Martino D, Marchese R, Aniello MS, Minafra B, Superbo M, et al. Quality of sleep in primary focal dystonia: a case-control study. *Eur J Neurol* (2010) 17:576–81. doi:10.1111/j.1468-1331.2009.02884.x
  49. Paus S, Gross J, Moll-Muller M, Hentschel F, Spottke A, Wabbels B, et al. Impaired sleep quality and restless legs syndrome in idiopathic focal dystonia: a controlled study. *J Neurol* (2011) 258:1835–40. doi:10.1007/s00415-011-6029-6
  50. Eichenseer SR, Stebbins GT, Comella CL. Beyond a motor disorder: a prospective evaluation of sleep quality in cervical dystonia. *Parkinsonism Relat Disord* (2014) 20:405–8. doi:10.1016/j.parkreldis.2014.01.004
  51. Trotti LM, Esper CD, Feustel PJ, Bliwise DL, Factor SA. Excessive daytime sleepiness in cervical dystonia. *Parkinsonism Relat Disord* (2009) 15:784–6. doi:10.1016/j.parkreldis.2009.04.007
  52. Romano R, Bertolino A, Gigante A, Martino D, Livrea P, Defazio G. Impaired cognitive functions in adult-onset primary cranial cervical dystonia. *Parkinsonism Relat Disord* (2014) 20:162–5. doi:10.1016/j.parkreldis.2013.10.008
  53. Hinse P, Lepow B, Humbert T, Lamparter U, Junge A, Emskotter T. Impairment of visuospatial function in idiopathic spasmodic torticollis. *J Neurol* (1996) 243:29–33. doi:10.1007/BF00878528
  54. Allam N, Frank JE, Pereira C, Tomaz C. Sustained attention in cranial dystonia patients treated with botulinum toxin. *Acta Neurol Scand* (2007) 116:196–200. doi:10.1111/j.1600-0404.2007.00862.x
  55. Conte A, Berardelli I, Ferrazzano G, Pasquini M, Berardelli A, Fabbrini G. Non-motor symptoms in patients with adult-onset focal dystonia: sensory and psychiatric disturbances. *Parkinsonism Relat Disord* (2016) 22(Suppl 1):S111–4. doi:10.1016/j.parkreldis.2015.09.001
  56. Hutchinson M, Kimmich O, Molloy A, Whelan R, Molloy F, Lynch T, et al. The endophenotype and the phenotype: temporal discrimination and adult-onset dystonia. *Mov Disord* (2013) 28:1766–74. doi:10.1002/mds.25676
  57. Jinnah HA, Berardelli A, Comella C, Defazio G, DeLong MR, Factor S, et al. The focal dystonias: current views and challenges for future research. *Mov Disord* (2013) 28:926–43. doi:10.1002/mds.25567
  58. Fuchs T, Saunders-Pullman R, Masuh I, Luciano MS, Raymond D, Factor S, et al. Mutations in GNAL cause primary torsion dystonia. *Nat Genet* (2013) 45:88–92. doi:10.1038/ng.2496
  59. Vemula SR, Puschmann A, Xiao J, Zhao Y, Rudzinska M, Frei KP, et al. Role of Galpha(olf) in familial and sporadic adult-onset primary dystonia. *Hum Mol Genet* (2013) 22:2510–9. doi:10.1093/hmg/ddt102
  60. Charlesworth G, Plagnol V, Holmstrom KM, Bras J, Sheerin UM, Preza E, et al. Mutations in ANO3 cause dominant craniocervical dystonia: ion channel implicated in pathogenesis. *Am J Hum Genet* (2012) 91:1041–50. doi:10.1016/j.ajhg.2012.10.024
  61. Delnooz C, MWIM H, MA T, van de Warrenburg BP. Paramedical treatment in primary dystonia: a systematic review. *Movement Disorders* (2009) 24:2187–98. doi:10.1002/mds.22608
  62. De Pauw J, Van der Velden K, Meirte J, Van Daele U, Truijens S, Cras P, et al. The effectiveness of physiotherapy for cervical dystonia: a systematic literature review. *J Neurol* (2014) 261:1857–65. doi:10.1007/s00415-013-7220-8
  63. Tassorelli C, Mancini F, Balloni L, Pacchetti C, Sandrini G, Nappi G, et al. Botulinum toxin and neuromotor rehabilitation: an integrated approach to idiopathic cervical dystonia. *Mov Disord* (2006) 21:2240–3. doi:10.1002/mds.21145
  64. El-Bahrawy M, El-Tamawy M, Shalaby N, Abdelalim A. Cervical dystonia: abnormal head posture and its relation to hand function. *Egypt J Neurol Psychiatr Neurosurg* (2009) 46:203–8.
  65. Boyce MJ, Canning CG, Mahant N, Morris J, Latimer J, Fung VS. Active exercise for individuals with cervical dystonia: a pilot randomized controlled trial. *Clin Rehabil* (2013) 27:226–35. doi:10.1177/0269215512456221
  66. Queiroz MA, Chien HF, Sekeff-Sallem FA, Barbosa ER. Physical therapy program for cervical dystonia: a study of 20 cases. *Funct Neurol* (2012) 27:187–92.
  67. Bleton JP. Physiotherapy of focal dystonia: a physiotherapist's personal experience. *Eur J Neurol* (2010) 17:107–12. doi:10.1111/j.1468-1331.2010.03061.x
  68. Dool JVD, Visser B, Koelman JHTM, Engelbert RHH, Tijssen MAJ. Cervical dystonia: effectiveness of a standardized physical therapy program; study design and protocol of a single blind randomized controlled trial. *Movement Disorders* (2013) 28(Suppl 1): S1–511.
  69. Quartarone A, Rizzo V, Morgante F. Clinical features of dystonia: a pathophysiological revisitation. *Curr Opin Neurol* (2008) 21:484–90. doi:10.1097/WCO.0b013e328307bf07
  70. Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: Implications for rehabilitation after brain damage. *J Speech Language Hearing Res* (2008) 51:S225–39. doi:10.1044/1092-4388(2008/018)
  71. Schmidt RA, Lee TD. *Motor Control and Learning: A Behavioral Emphasis*. Champaign, IL: Human Kinetics (1999).
  72. Shea CH, Shebilske WL, Worchel S. *Motor Learning and Control*. Englewood Cliffs, NJ: Prentice-Hall (1993).
  73. Shea JB, Morgan RL. Contextual interference effects on the acquisition, retention, and transfer of a motor skill. *J Exp Psychol Human Learning Memory* (1979) 5:179–87. doi:10.1037/0278-7393.5.2.179
  74. Bleton JP, Vidailhet M, Bourdain F, Ducorps A, Schwartz D, Delmaire C, et al. Somatosensory cortical remodelling after rehabilitation and clinical benefit of in writer's cramp. *J Neurol Neurosurg Psychiatry* (2011) 82:574–7. doi:10.1136/jnnp.2009.192476

**Conflict of Interest Statement:** MC, Advisory board: Medtronic, Boston Scientific, is co-inventor on a patent application relevant to Deep Brain Stimulation (2014). Speaking fees: Abbvie, Medtronic, Boston Scientific, ECMT. Grant: Stichting Parkinson Fonds. MS: Grants: University Medical Centre Groningen, Stichting Wetenschapsfonds Dystonie Vereniging. JD: Grants: Dutch organizations in scientific research, the Fonds NutsOhra, Jacques and Gloria Gossweiler foundation and Stichting Wetenschapsfonds Dystonie Vereniging. JV: advisory boards: Boston Scientific, Medtronic; grant support: Boston Scientific, Medtronic; Speaking fees: Boston Scientific, Medtronic, St. Jude, UCB, TEVA, and Allergan. MT: Grants: Netherlands organization for scientific research-NWO, Medium, Fonds Nuts-Ohra,

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