REVIEW ARTICLE

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Does botulinum toxin type A treatment influence non-motor symptoms in cervical dystonia patients? A systematic review

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ABSTRACT

The effect of botulinum toxin A (BoNTA) on non-motor symptoms (NMS) in patients with cervical dystonia remains an area of significant clinical interest, given the profound impact of these symptoms on patients' quality of life. While the therapeutic efficacy of BoNTA in alleviating motor symptoms of cervical dystonia is well established, its impact on NMS such as depression, anxiety disorder, and sleep disturbance requires further investigation.

This systematic review synthesizes the latest evidence on the effects of BoNTA on these selected non-motor symptoms.

A comprehensive search of the PubMed, Web of Science, and Scopus databases identified 266 articles, of which eight studies met our strict inclusion criteria. Pre- and post-intervention changes in depression, anxiety, and sleep disturbance were assessed in a total of 280 adult patients with cervical dystonia treated with BoNTA.

The results indicate that BoNTA has a positive effect on depressive symptoms, with most studies showing a statistically significant improvement after treatment. Similarly, studies are reporting significant reductions in anxiety scores following BoNTA treatment. However, the effects of this treatment method on sleep disturbances were less conclusive, with none of the reviewed studies showing significant improvements in sleep quality or daytime sleepiness.

The results highlight the potential of BoNTA to positively influence non-motor symptoms, particularly depression and anxiety, in patients with cervical dystonia, although its effects on sleep remain unclear. These findings underscore the need for further research to fully understand the mechanisms underlying the non-motor effects of BoNTA and to develop comprehensive treatment strategies.

Keywords: cervical dystonia, non-motor symptoms, depression, anxiety, sleep, botulinum toxin type A, BoNT, quality of life

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Introduction

The current definition of dystonia, established in 2013 by Albanese et al., describes it as "a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation" [1].

However, in addition to motor symptoms, non-motor symptoms (NMS) of dystonia are recognized as meaningful aspects of the disease and important determinants of quality of life. NMS of dystonia include sleep-related disturbances, psychiatric disorders such as anxiety disorder and depression, decreased cognitive functions, fatigue, sexual dysfunction, and, most commonly, pain [2, 3]. Proper management of non-motor symptoms is an essential component of integrated care for patients with dystonia. Despite a growing number of publications on non-motor symptoms of cervical dystonia

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[3–5], only a few studies have focused specifically on the effects of treatment on NMS. The first-line treatment for motor symptoms of cervical dystonia is botulinum toxin injection into the affected muscles. It has been well documented that this method is effective in muscle relaxation and alleviation of abnormal movements or postures [6]. In addition, it has been shown that some of the NMS observed in patients with cervical dystonia (especially pain) improve after BoNTA [7–10].

The implications of these findings are profound. Pain is a predominant symptom that significantly impacts upon the quality of life of dystonia patients. Pain relief with BoNTA treatment significantly improves their quality of life. Pain is perceived as a core symptom of dystonia in addition to the motor symptoms [9], but the mechanisms of pain in dystonia are complex. There is a component due to prolonged muscle contraction, but there are also non-muscle-based mechanisms, and it has been postulated that the genesis of pain is multifactorial [10]. There is no consensus as to whether pain should be considered a pure non-motor feature of dystonia. Due to this inconsistency, pain was not included in this review.

The studies that have focused on quality of life, cognition, fatigue, and sexual dysfunction have lacked consistency in their methodology, particularly in the scales used to assess outcomes. In addition, there have been only a limited number of studies on the effect of BoNTA treatment on cognition, fatigue and sexual dysfunction. It was not possible to make a comparison between the studies in terms of following an established methodology.

However, the relationship between botulinum toxin injections and improvements in other non-motor symptoms such as sleep disturbances, depression and anxiety disorder, remains unclear and requires further research to elucidate the full spectrum of BoNTA's therapeutic potential.

Depression is one of the most frequent psychiatric disorders in patients with cervical dystonia [11]. It can occur as a response to altered perceptions of a distorted body image with physical limitations, as a response to chronic pain, and as a result of biological mechanisms associated with the disease itself. Patients with depression often experience reduced motivation for treatment, which can lead to poorer compliance and clinical outcomes [12]. In addition, depression affects patients' ability to engage in social and occupational activities, leading to social isolation and a significant decline in quality of life.

Anxiety disorder is another common condition that significantly affects patients' quality of life [11]. In patients with cervical dystonia, anxiety may result from the abnormal posture and unpredictable muscle contractions that cause not only pain, but also head and neck movements that are noticeable in society and thus lead to embarrassment and fear of social stigma. This anxiety often leads to isolation and thus a further deterioration in mental health, often co-occurring with depression [13]. Prolonged anxiety also affects cognitive functioning and thus the ability to cope with daily activities.

Sleep disturbances such as insomnia, sleep fragmentation, or excessive daytime sleepiness are commonly reported by patients with cervical dystonia [14]. Sleep plays a critical role in physical and mental recovery, and its disruption can have a wide range of health effects. Insufficient or poor-quality sleep can exacerbate pain perception, reduce coping skills, and impair cognitive function. In addition, sleep disorders can affect mood regulation, leading to increased levels of depression and anxiety, contributing to a vicious cycle of worsening symptoms and a further diminishment in quality of life.

These NMS are often interrelated, creating a complex interplay that exacerbates the burden of the disease. Addressing these symptoms through comprehensive treatment approaches is critical to improving the overall well-being of patients [11]. Therefore, studying the influence of botulinum toxin treatment on NMS has become an important focus of dystonia research.

The aim of this study was to review the current state of scientific evidence on the influence of BoNTA treatment on selected non-motor symptoms such as depression, anxiety disorder and sleep-related disturbances in patients with cervical dystonia. We also looked for areas where further research is needed.

Material and methods

This review was carried out in accordance with PRISMA guidelines (Fig. 1). The approval of a bioethics committee was not required. The study was registered in the international database PROSPERO (https://www.crd.york.ac.uk/prospero/) with the registration ID: CRD42023492198.

A PubMed search for the terms: 'cervical dystonia' and 'botulinum toxin' and ('non-motor symptoms' or 'anxiety' or 'depression' or 'sleep') was performed. Then a search with the same algorithm was conducted in the Web of Science and Scopus databases. The reference lists were also searched for additional publications. These searches were performed simultaneously and independently by two authors, MD and AP, and were completed by 30 April, 2024.

The following inclusion criteria were used:

1) original studies published in English
2) adult patients diagnosed with cervical dystonia who were treated with BoNTA
3) pre- and post-interventional assessment of one or more of the following non-motor symptoms of cervical dystonia: anxiety, depression, and/or sleep-related disturbances.

The exclusion criteria were:

1) lack of pharmacological intervention or an intervention with botulinum toxin other than type A
2) lack of pre- and post-intervention assessment of depression, anxiety or sleep-related disturbances.

After a primary search, duplicates were removed. Then the publications were checked for inclusion and exclusion

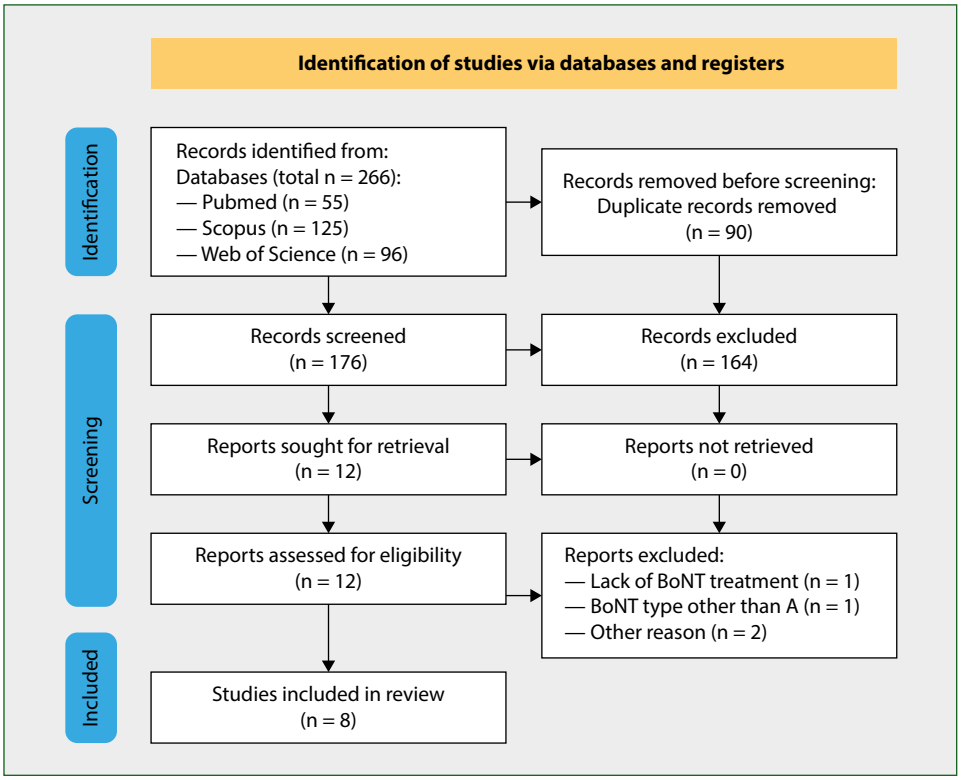

Figure 1. Detailed process of including studies into the review, according to PRISMA

criteria and the following data was extracted from the included articles: first author, year of publication, study population characteristics, study design, methods (types of inventories and questionnaires), and results.

The Quality Assessment Tool for Quantitative Studies (QATQS) was employed to evaluate the methodological quality of the included studies. The evaluation was conducted by two authors, MD and AP. Any disagreements were resolved by a third author, KH. This tool assesses eight domains: selection bias, study design, confounders, blinding, data collection methods, withdrawals and dropouts, intervention integrity, and analysis. For a study with one group, the confounders section was rated as 1. Each domain could be rated as weak, moderate, or strong. A study was classified as strong if no domain was rated as weak; if one domain was rated as weak, the study was rated as moderate. A study was deemed weak if two or more domains were rated as weak.

Results

From a total of 266 articles reviewed, 90 duplicates were eliminated. Of the 176 remaining studies, only eight were included. The remaining 168 papers did not meet the inclusion criteria, mostly due to a lack of a second assessment after botulinum toxin treatment. The other reasons for exclusion were: another type of dystonia (i.e. not cervical dystonia), and another type of botulinum toxin (other than type A).

Figure 1 (PRISMA) illustrates the detailed process of study inclusion for this review. Table 1 illustrates the group characteristics and the main findings of the included studies. Table 2 and Figure 2 illustrate the quality assessment of the included studies.

Quality assessment

The methodological quality of all included studies is shown in Table 2. Two studies were rated as 'strong', four as 'moderate', and two as 'weak'. The section on data collection was rated the highest and the section on withdrawals and dropouts was rated the lowest. It is worth mentioning that few publications have addressed the effect of botulinum toxin on non-motor symptoms in patients with cervical dystonia. Of the included publications, two were rated low quality, four were rated moderate quality, and two were rated high quality. However, it is important to note some challenges in designing this type of study that were often described by the authors. One limitation was the lack of a control group — in only half of the studies did the authors relate their results to a healthy population. Only in two studies did the authors refer to dropouts or other reasons for patients dropping out of the study, and it was not clearly stated whether all of the participants were evaluated at two separate time points.

Table 1. Studies showing the effect of BoNTA on depression, anxiety disorder and on sleep-related disturbances (sleep quality and/or daytime sleepiness) in cervical dystonia

Study	Sample size (women)	Mean age	Follow-up [in weeks]	Tests	Main findings	Final quality of study
Depression						
Muller et al. 2002	57 (30)	53	4	BDS (BDI)	BDS total score improved by a mean of 17% after BoNTA; significant improvement (p = 0.004)	1
Slawek et al. 2007	83 (51)	49.9	4	MADRS	MADRS score significantly lower (p < 0.001) after BoNTA (mean value 21.9 at baseline and 16.9 at follow up)	2
Karakulova et al. 2017	48 (32)	47.6	4	HAM-D	Levels of depression decreased significantly (p < 0.05) after BoNTA (HAM-D at baseline 15.0 ± 6.3 points, 11.30 ± 3.32 points at follow up)	3
Ceylan et al. 2019	30 (20)	49	8	BDS, HDS	Improvements in BDS (p = 0.178) and HDS (p = 0.183) after BoNTA noted (BDS at baseline 11.13 ± 8.68 and 9.70 ± 7.90 at follow up; HDS at baseline 5.73 ± 4.40 and 4.96 ± 3.63 at follow up)	3
Costanzo et al. 2021	45 (28)	58.5	4	HAM-D	BoNTA significantly reduced HAM-D scores (p = 0.001; Z = 3.1); lack of correlation between motor and non-motor symptoms improvement after BoNTA	2
Dec-Cwiek et al. 2023	17 (13)	53.5	6	HDS	No statistically significant differences after BoNTA in HDS	2
Anxiety disorder						
Karakulova et al. 2017	48 (32)	47.6	4	HAM-A, SHT	Levels of anxiety in HAM-A decreased slightly; SHT significantly reduced in state-anxiety and slightly reduced in trait-anxiety after BoNTA (SHT state anxiety from 51.42 ± 13.55 at baseline to 37.2 ± 7.5 at follow up; trait anxiety from 54.18 ± 12.19 at baseline to 49.8 ± 10.9 at follow up)	3
Ceylan et al. 2019	30 (20)	49	8	STAI-I, STAI-II, HAS	Statistically significant improvement in terms of anxiety in STAI-I (p = 0.002) and STAI-II (p = 0.01) after BoNTA noted (STAI-1 at baseline 40.00 ± 7.68 and 36.06 ± 8.19 at follow up; STAI-2 at baseline 43.76 ± 8.70 and 40.66 ± 7.97 at follow up; HAS at baseline 6.90 ± 4.63 and 5.86 ± 3.22 at follow up)	3
Costanzo et al. 2021	45 (28)	58.5	4	HAM-A	BoNTA significantly reduced HAM-A scores (p = 0.0001; Z = 3.86); lack of correlation between motor and non-motor symptoms improvement after BoNTA	2
Dec-Cwiek et al. 2023	17 (13)	53.5	6	HAS	No statistically significant differences after BoNTA in HAS	2
Sugar et al. 2023	60 (43)	60.6	6	STAI-S, STAI-T	Improvements in STAI-total score (p = 0.007), STAI-T (p = 0.001) and STAI-S (p = 0.01) noted from baseline to six weeks after BoNTA (baseline STAI-total mean score 73.47 ± 30.05 and MD = –10.37 at follow up; STAI-T MD = –5.15 and STAI-S MD = –5.22)	2
Sleep-related disturbances						
Eichenseer et. al. 2014	48 (38)	62	6–8	PSQI, ESS	No significant change in sleep quality (p = 0.41) or excessive daytime sleepiness (p = 0.083) after BoNTA (PSQI at baseline 7.50 ± 4.2 and 7.46 ± 4.3 at follow up; ESS at baseline 5.04 ± 4.0 and 4.60 ± 3.8 at follow up)	1
Costanzo et al. 2021	45 (28)	58.5	4	PSQI, ESS	BoNTA did NOT modify sleep-related disorders — PSQI (p = 0.06; Z = 1.85), ESS (p = 0.8; Z = 0.13)	2
Dec-Cwiek et al. 2023	17 (13)	53.5	6	PSQI	No statistically significant differences after BoNTA in PSQI	2

BDS — Beck Depression Scale (BDI — Beck Depression Inventory); HDS — Hospital Depression Scale; HAM-D — Hamilton Depression Rating Scale; MADRS — Montgomery-Asberg Depression Rating Scale; STAI-I (S) and STAI-II (T) — State (I/S) and Trait (II/T) Anxiety Inventory; HAS — Hospital Anxiety Scale; HAM-A — Hamilton Anxiety Rating Scale; SHT — Spielberger-Hanin test; MD — mean difference; PSQI — Pittsburgh Sleep Quality Index; ESS — Epworth Sleepiness Scale

Table 2. Methodological quality of each study using QATQS

Author and year	Selection bias	Design	Confounders	Blinding	Data collection	Withdrawals and dropouts	Total
Ceylan et al. 2019	3	2	1	2	1	3	3
Costanzo et al. 2021	2	2	1	1	1	3	2
Dec-Cwiek et al. 2023	3	1	1	1	1	3	2
Karakulova et al. 2017	2	2	3	2	1	3	3
Muller et al. 2002	2	2	1	2	1	2	1
Slawek et al. 2007	2	2	1	2	1	3	2
Sugar et al. 2023	1	2	1	1	1	3	2
Eichenseer et al. 2014	1	2	1	2	1	1	1

1 — strong; 2 — moderate; 3 — weak

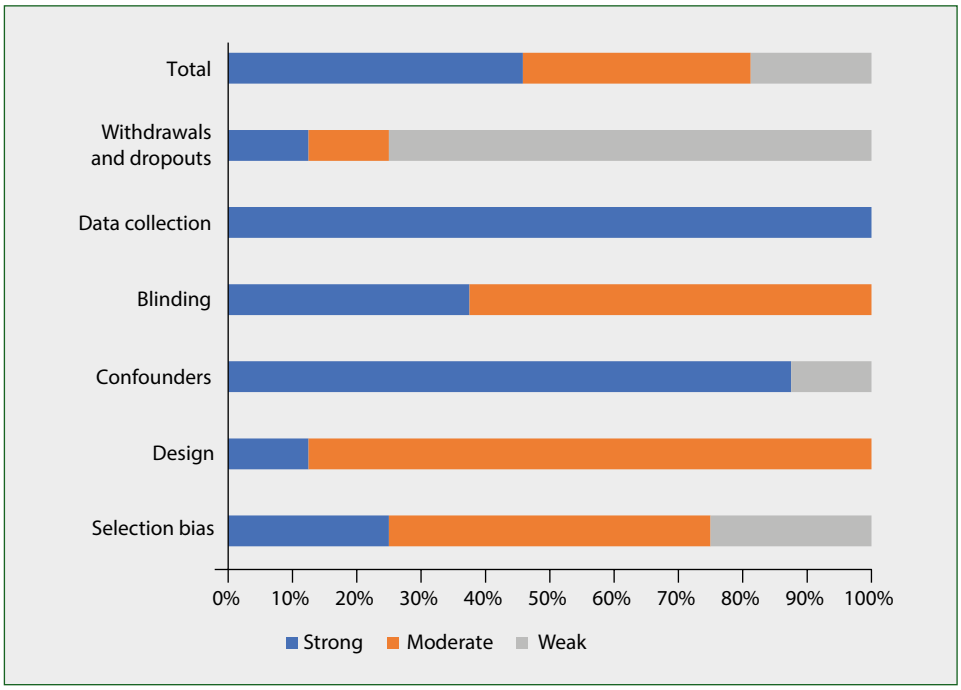

Figure 2. Detailed quality assessment of each reviewed study presented as a percentage

Depression

A total of 280 patients were included in the six studies that examined the effect of BoNTA treatment on depression. The studies assessing the influence of BoNTA on depression in patients with cervical dystonia consisted mostly of self-assessment inventories such as BDI — Beck Depression Inventory (also known as BDS, Beck Depression Scale). These tools are widely recognized for their reliability and validity in measuring depressive symptoms.

In a study by Ceylan et al. [11] among 30 patients with cervical dystonia, 46.7% were found to have depression in baseline examination. In a second assessment eight weeks after BoNTA treatment, there was an improvement in both the BDS ($p = 0.178$) and the Hospital Depression Scale (HDS; $p = 0.183$). Although these results did not reach conventional levels of statistical significance, the observed trends suggest a potentially beneficial effect of BoNTA on depressive symptoms.

Even better evidence for the efficacy of BoNTA in reducing depressive symptoms was found in the study by Muller et al. [15]. In this study, involving 57 patients with cervical dystonia, the BDI total score improved by a mean of 17% ($p = 0.004$) at the follow up visit (four weeks after BoNTA treatment). This improvement was correlated with reduced neck pain, and it highlights the potential of BoNTA to positively influence mood, probably through mechanisms involving pain reduction and improved motor function.

Similarly, Slawek et al. [16] showed a statistically significant reduction in depressive symptoms, as measured by the

Montgomery-Asberg Depression Rating Scale (MADRS), four weeks after the BoNTA injection ($p < 0.001$). This study also identified depression to be the most predictive factor for poor Health Related Quality of Life (HRQoL) in patients with cervical dystonia.

Further supporting these findings, the studies by Costanzo et al. [7] and Karakulova et al. [17] reported statistically significant improvements in Hamilton Depression Rating Scale (HAM-D; $p = 0.001$ and $p < 0.05$, respectively). Costanzo et al. [7] also provided valuable insights into the relationship between motor and non-motor symptoms, showing no significant time correlation between motor and non-motor BoNTA-induced improvements. This suggests that the beneficial effects of BoNTA on depression might be mediated through different pathways than those affecting motor symptoms.

However, it is important to note that out of six reviewed studies concerning depression, only one study (by Dec-Cwiek et al. [18]) did not find a significant improvement in depression scales 4–8 weeks after BoNTA treatment. This discrepancy highlights the variability in patients' responses, and underlines the need for further research to identify the factors that play a major role in the influence of BoNTA on depressive symptoms.

Anxiety disorder

Among the analyzed studies, five concerned anxiety disorder, including a total of 200 patients. A distinction between state and trait anxiety was made in studies by Ceylan et al. [11] and Sugar et al. [13]. Both these studies reported improvements in the anxiety measures in the second assessment following BoNTA treatment. Ceylan et al. additionally evaluated anxiety using the Hospital Anxiety Scale (HAS). Interestingly, severe anxiety at baseline was found in 26.6% of patients according to HAS inventory, a similar figure to the 30% for STAI-I (state anxiety). An improvement after BoNTA in HAS was noted with significance of 0.112, whereas in STAI-I score an improvement was noted with significance of $p = 0.002$. This difference is due to the different survey methods used.

Two of the reviewed studies used the Hamilton Anxiety Rating Scale (HAM-A), which is a clinician-administered questionnaire rather than a self-report inventory. In the study by Costanzo et al. [7], BoNTA treatment significantly reduced HAM-A scores ($p = 0.0001$), although no correlation was found between motor and non-motor improvement after the injections. Similarly, Karakulova et al. [17] also reported a slight decrease in HAM-A scale. However, the decrease in the self-reported state-anxiety score was significant but in the trait-anxiety score the reduction was minor. Unfortunately, the level of significance was not revealed in the study. In the research paper by Dec-Cwiek et al. [18], no statistically significant differences in HAS, which is a self-reported scale, were found.

The improvements in anxiety symptoms observed in these studies underline the potential benefits of BoNTA treatment beyond its primary motor effects. The significant reduction in state anxiety (STAI-I) observed in the Ceylan et al. [11] study suggests that BoNTA may help alleviate immediate anxiety symptoms that are often exacerbated by the physical manifestations of cervical dystonia. In contrast, the moderate improvement in trait anxiety suggests that while BoNTA may reduce situational anxiety, its effect on long-term, stable anxiety traits may be less pronounced.

The study by Costanzo et al. [7] highlights an important aspect of BoNTA treatment i.e. the dissociation between improvements in motor and non-motor symptoms. This finding suggests that the mechanisms by which BoNTA alleviates anxiety may be different from those responsible for its effects on motor symptoms, possibly involving direct or indirect modulation of neurotransmitter systems involved in anxiety regulation.

Sleep

Only three studies, including 110 patients, met the inclusion criteria for sleep disturbances, although the assessment methods and results for the sleep issue were more consistent across the reviewed studies. The Pittsburgh Sleep Quality Index (PSQI) questionnaire was used in all included studies [7, 14, 18]. In addition, the studies by Costanzo et al. and Eichenseer et al. [14] also assessed daytime sleepiness using the Epworth Sleepiness Scale (ESS). The PSQI is a comprehensive tool that assesses several dimensions of sleep quality, including duration, disturbances, latency, and efficiency. No significant improvements in PSQI scores were observed in the studies reviewed. Similarly, no significant effect of BoNTA treatment on the overall level of daytime sleepiness was found in the ESS.

These results seem surprising when combined with the improvements observed in depressive and anxiety symptoms, given that sleep disturbance is also a major feature of these disorders. Therefore the mechanism of BoNT effectiveness in various NMS must be complex.

Discussion

Non-motor symptoms of dystonia are recognized as an important aspect of the disease and a clear determinant of well-being. Ray et al. [3] in their review analyzed the literature on non-motor symptoms of dystonia, excluding studies that evaluated symptoms after botulinum toxin injections. Based on 61 studies analyzed, those authors listed the most common non-motor symptoms associated with dystonia as: pain, anxiety, depression, cognitive dysfunction, restless leg syndrome, poor sleep, and excessive daytime sleepiness. Other studies are consistent with these findings. Pain, depression, anxiety, and sleep disturbance appear to be the most important, to have the greatest impact on patients' quality of life [4, 5, 7, 12], and to have a great influence on the effectiveness of treatment and its long-term continuation [8]. As botulinum toxin is the treatment of choice for motor symptoms of dystonia, it can be hypothesized that this method could also affect non-motor symptoms.

Pathophysiology of NMS and hypothesized mechanism of action of BoNTA in NMS

According to Albanese et al. [6], in dystonia "the involuntary movement is a product of a resultant network dysfunction involving brainstem, basal ganglia, cerebellum, and cortex". It has been suggested that the role of the basal ganglia in cervical dystonia extends beyond motor control, affecting cognitive and sensory functions as well as sensorimotor integration [19]. Functional magnetic resonance imaging (fMRI) is a method of the utmost importance in explaining the pathophysiology of dystonia. Nevrly et al. [20] used fMRI to investigate the involvement of the basal ganglia and thalamus and functional abnormalities in the sensorimotor cortex in dystonia patients. Furthermore, changes in the activation of the sensorimotor network after BoNTA injections were demonstrated. Stamelou et al. [21] hypothesized that the NMS of dystonia may be explained by a similar pathophysiology that underlies the motor symptoms. Genetic susceptibility may be responsible for neurochemical and functional imbalance in the basal ganglia, that could cause a widespread loss of inhibition and increased plasticity, which might result in the non-motor features of primary dystonia [21].

Based on current knowledge, cortical regions, particularly prefrontal and frontal regions, and cortico-striatal circuits may be involved in the psychiatric and cognitive symptoms of dystonia [22]. However, further studies are needed to confirm these findings and to explore the underlying brain networks.

Depression

Depressive symptoms and anxiety are the most common psychiatric symptoms associated with cervical dystonia [11, 22]. In a meta-analysis by Medina Escobar et al., the prevalence of depressive symptoms or depressive disorders was 31.5 % for cervical dystonia, and 29.2 % for cranial dystonia. The authors concluded that the prevalence of depressive symptoms was higher when evaluated via rating scales than via structured interviews. However, both depression and anxiety severity improved with both clinician and self-report measures [23].

Despite the known common co-occurrence with cervical dystonia, there have been very few studies on depressive symptoms in dystonia in correlation with symptomatic treatment. Several papers have examined the relationship between the severity of depressive symptoms and motor symptoms [4, 24, 25], but studies on the effect of BoNTA treatment on depression severity are lacking.

In this current review, we analyzed six studies on the effect of botulinum toxin injections on depressive symptoms severity. Only one of the studies did not show a clear improvement after BoNTA treatment [18]. The exact pathomechanism of this trend is not yet understood, but given the fact that cervical dystonia is due to brain network imbalance, it has been suggested that neuronal connectivity rebalances and modulates neurotransmitter levels, especially in striatal dopaminergic and serotonergic pathways [26, 27].

Anxiety

Increased levels of anxiety have been reported in most of the literature on anxiety in dystonia [5, 7, 11, 13, 24–26, 28–30]. Many studies on anxiety in dystonia have differentiated between state and trait anxiety, using STAI-I (S) and STAI-II (T) inventories. State anxiety is associated with the response of the autonomic nervous system, and it is dependent on specific situations of daily life. Trait anxiety is defined as individual and personal character in response to a stressful stimulus.

BoNTA treatment has shown effectiveness in reducing both motor symptoms and anxiety levels, as demonstrated by the reviewed studies. Of the five studies specifically focused on anxiety, four reported statistically significant improvements in anxiety measures post-treatment. The improvements were particularly notable in state anxiety, suggesting that BoNTA may help alleviate anxiety that is situationally triggered, possibly through mechanisms distinct from those affecting motor function. However, one study did not show significant changes in anxiety scales, highlighting the variability in response and the influence of assessment methods. Only one study found no statistically significant differences, and this one used HAS inventory pre- and post-treatment [18]. This discrepancy may be attributable to the self-reported nature of the HAS inventory, suggesting that subjective perceptions of anxiety improvement might differ from those assessed by clinicians or other standardized measures. The mechanisms underlying BoNTA's effect on anxiety may differ from those responsible for its motor effects, possibly involving modulation of the secretion of neurotransmitters (such as monoamines and polypeptides) that play a role in anxiety regulation [13].

The evidence supports the potential of BoNTA to reduce anxiety in patients with dystonia, although further research is needed to fully understand its pathways.

Sleep

Sleep disturbances include difficulty falling asleep, changes in sleep quality and duration, and increased daytime sleepiness. These problems are common in dystonic patients for a number of reasons, the most important of which are postural changes and intermittent muscle contractions that persist throughout the night and affect sleep quality for physical reasons. Pain that usually accompanies dystonic movements, and psychiatric disorders such as depression and anxiety which often coexist in dystonia, are also predisposing factors for sleep disturbance.

Our analysis of the effect of BoNTA on sleep disturbance showed no significant improvement in sleep quality after treatment. All studies used the Pittsburgh Sleep Quality Index (PSQI) to assess different dimensions of sleep, such as duration, disturbances, latency, and efficiency [7, 14, 18]. In addition, the studies by Costanzo et al. [7] and Eichenseer et al. [14] used the Epworth Sleepiness Scale (ESS) to measure daytime sleepiness. Despite the comprehensive assessment methods, neither the PSQI nor the ESS scores showed significant changes

after BoNTA treatment. In the analyzed studies, the level of sleep disturbance was not correlated with motor improvement after BoNTA treatment, suggesting that the mechanism of this symptom is not due solely to the burden of muscle contraction and improper head posture.

These findings are somewhat unexpected, given the concurrent improvements in depressive and anxiety symptoms observed in related studies, where sleep disturbance is often a significant feature.

This discrepancy suggests that the mechanisms by which BoNTA exerts its effects on non-motor symptoms, such as mood and anxiety, may differ from those affecting sleep. The complexity of the effects of botulinum toxin on different neurological and neuropsychiatric symptoms requires further investigation to better understand its role and potential in the treatment of diverse aspects of dystonia.

Limitations

This study has several limitations. We only included articles on depression, anxiety, and sleep disturbance, which are the most common non-motor symptoms of dystonia. The rating scales were not always consistent, which is a clear indication that new consistent, comprehensive, and universally accepted rating scales are needed. Also the number of included studies was small, which may limit the generalizability of the results.

Conclusions

The observation of patients with cervical dystonia treated with BoNTA led to the conclusion that this method affects not only motor, but also non-motor, symptoms [31–33]. Although physical symptoms can be effectively treated with BoNTA, non-motor symptoms and psychiatric comorbidities appear to be more complex and difficult to manage [11, 34].

This review of the literature evaluating the effect of BoNTA treatment on depressive symptoms, anxiety and sleep disturbances in patients with cervical dystonia shows a generally positive effect, although the results are not consistent for all symptoms. There is a need for large scale prospective studies based on unified validated scales that can be performed in multiple dystonia centers around the world.

Article information

Authors' contributions: *MD: concept, data curation, formal analysis, investigation, methodology, writing original draft; AP: data curation, formal analysis, investigation, methodology, writing — review & editing; AD: project administration, resources, writing — review & editing; KH: investigation, methodology, supervision, writing — review & editing.*

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