• Clinical Research •

Correlation between blepharospasm and psychological diseases: the anxiety, depression and sleep disorder study

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Abstract

● **AIM:** To investigate the relationship between benign essential blepharospasm (BEB) symptoms and depression/anxiety/sleep disorder in a prospective manner and to determine whether treatment the BEB with botulinum toxin type A (BoNT/A) can impact psychological symptoms.

● **METHODS:** This prospective interventional case series recruited 61 adults with evidence of BEB. Patients were administered the Jankovic Rating Scale (JRS), the Blepharospasm Disability Index (BSDI), Personal Health Questionnaire Depression Scale (PHQ-8), Generalized Anxiety Disorder 7-item scale (GAD-7) and the Athens insomnia scale (AIS) to evaluate the severity of BEB symptoms, depression, anxiety and sleep disorder before and 1wk, 1, 3mo after the BoNTA treatment. Statistical analysis was performed to assess the relationships between changes in the survey scores.

● **RESULTS:** The mean score for JRS, BSDI, PHQ-8, and GAD-7 improved significantly (P<0.0001), respectively, compared to the initial visit at follow-up. At baseline, worse BSDI scores were correlated with worse GAD-7 and PHQ-8, but not with worse AIS. At 1mo follow-up visit, there was no correlation between change in BSDI and PHQ-8/AIS, the change in GAD-7 showed a mild association with change in BSDI. The change in BSDI was correlated with the change in both PHQ-8 and GAD-7 in the subgroup of patients without a prior diagnosis of depression or anxiety. Patient satisfaction with BoNT/A treatment reached the highest at 1mo of follow-up (83.6%, 51/61).

● **CONCLUSION:** BEB may lead to psychological diseases. BoNT/A can significantly improve motor and non-motor symptoms of BEB, which emphasize the effectiveness of BoNT/A and therefore pave the way for its use in the field of psychiatry. However, further research is needed to confirm these findings and understand the underlying mechanisms.

● **KEYWORDS:** blepharospasm; psychological diseases; sleep disorder; botulinum toxin type A

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INTRODUCTION

Benign essential blepharospasm (BEB) is a chronic idiopathic, recurrent and progressive disease that occurs primarily in both eyes, manifested in an involuntary spasm of the muscles around the eyes, resulting in an uncontrollable narrowing or even closure of the fissure of the eyelid[1]. Although patients with BEB have no pain, it can cause social or psychological dysfunction and make patients feel difficult to drive, read and work. BEB affect approximately 32 per 100 000 people, and the affect can persist throughout life[2]. The pathogenesis of BEB is unclear, but it has been hypothesized that it is caused by impaired control of blink circuit as a result of the cortico-striato-thalamo-cortical circuits[3]. BEB has been found to have a serious negative impact on patient well-being, productivity at work, and finances. In the past, the Jankovic Rating Scale (JRS) was used as a standard physician rating scale that quantifies the typical symptoms of BEB[4]. However, the scale does not directly assess the potential impact on patient quality of life. Therefore, a new patient evaluation scale for specific diseases, the Blepharospasm Disability Index (BSDI), was developed to supplement JRS as the evaluation scale reported by patients, which can evaluate the activities of a single patient, such as reading and driving[5].

However, despite the availability of these objective tests, ocular symptoms do not always correlate with test results in

BEB patients. Recently, many studies focus on the ocular diseases and psychology, such as dry eye and depression–anxiety[6]. According to the data released by the WHO, about 280 million people in the world are estimated to suffer from depression. The psychological and neurological factors associated with BEB are far less studied, but have recently gained more interest. In addition to motor symptoms, patients with BEB may have non-motor features, affecting patient quality of life, social interactions, employment status, and may lead to depression/anxiety and sleep disorder[7]. On the other hand, anxiety, depression, and sleep disorder can also affect the motor symptoms of BEB.

Existing therapies of BEB such as bilateral globus pallidus stimulation and dipraglurant produce only partial benefits[8-9], botulinum toxin type A (BoNT/A) is still considered as the best choice of therapy for BEB[10]. Based on a review of open and controlled trials, BoNT/A successfully treats approximately 90% of BEB patients[11]. However, whether BoNT/A injection can also improve depression/anxiety and sleep disorder in BEB patients is not known.

Therefore, the objectives of our study are to further investigate the relationship between BEB and depression/anxiety/sleep disorder prospectively and to determine whether treatment of BEB with BoNT/A can affect depression/anxiety symptoms and sleep disorder.

SUBJECTS AND METHODS

Ethical Approval Before study enrollment, all patients provided informed consent to participate in the research. The study was in accordance with the tenets of the Declaration of Helsinki, and was approved by the Institutional Review Boards of the Second Affiliated Hospital, Zhejiang University School of Medicine (No.2020691).

Subjects This prospective study included 61 BEB patients (16 males and 45 females) who received BoNT/A injection therapy. All patients must have had symptoms of BEB for more than 6mo according to this classification system.

Ocular and systemic diseases that can lead to depression, anxiety and sleep disorder were recorded, including glaucoma, age-related macular degeneration, visual acuity of 20/200 or worse, chronic obstructive pulmonary disease, psychosis, cardio cerebral diseases, loss of limb, connective tissue diseases and dialysis dependence. The preexisting diagnosis of depression, anxiety, and sleep disorders was recorded and the medical treatment of these conditions was also noted. In addition, we also excluded the impact of environment, family and work on patients' emotions.

Benign Essential Blepharospasm Evaluation A diagnosis of BEB was established using the JRS[12]: In terms of severity, 0=no spasm; 1=mild spasm, rarely noticeable; 2=mild spasm, without dysfunction; 3=moderate spasm, with moderate dysfunction; 4=severe, incapacitating spasm. In terms of frequency, 0=no spasms, 1=increased blinks, 2=mild spasms of the eyelid and forced closure of the eyelid for more than a second; 3=the eyelid is forcibly closed for more than a second, but can remain open 50% of the time; 4=functional blindness, an inability to stay open for more than 50% of the waking time, forcing closure. Thus, the total score of JRS is 8.

BSDI includes six items: driving, reading, watching TV, shopping, walking and daily life. For each item, 0=no handicap, 1=mild handicap, 2=moderate handicap, 3=severe handicap, 4=no ability to perform the activity at all. If an item does not apply to a patient, the item should be removed. The final score is the average score of all applicable activities, so the score range of BSDI is 0-4.

Depression/Anxiety/Sleep Disorder Evaluation Depression and anxiety symptoms were performed using the validated Personal Health Questionnaire Depression Scale (PHQ-8) and the Generalized Anxiety Disorder 7 item scale (GAD-7) questionnaires[12]. The PHQ-8 has 8 items to evaluate depression with a total score of 24. GAD-7 has 7 items to evaluate anxiety with a total score of 21. For both tests, cut-points of 5, 10, and 15 as mild, moderate, and severe levels of depressive or anxiety symptoms. A score of 10 or greater indicating a clinically significant condition, and a score of 15 and greater warrants active treatment.

Sleep disorders were performed using the Athens Insomnia Scale (AIS). The severity criteria for AIS are capable of categorizing insomnia severity as follows: absence of insomnia (0-5), mild insomnia (6-9), moderate insomnia (10-15), and severe insomnia (16-24).

Treatment and Follow-up Patients were treated with on a botulinum toxin A (BoNT/A, Allergan, Irvine, California, USA) applications on the orbicularis oculi and glabellar complex. BoNT/A reconstitution and applications were carried out by a single investigator, according to a standardized application protocol: Each vial was reconstituted immediately before application with normal saline without preservatives to obtain a final concentration of 50 U/mL. An 30G needle were used for application on orbicularis oculi and glabellar complex. Patients were evaluated the JRS, BSDI, PHQ-8, GAD-7 and AIS surveys before BoNT/A treatment, at their 1wk, 1, and 3mo follow-up visit, subjects were again administered these surveys. The same clinicians obtained objective measures stated above.

Treatment Satisfaction Patients used a digital rating scale of 1 to 10 to score their current satisfaction with BoNT/A treatment, of which 1 was completely dissatisfied and 10 was very satisfied. Patients were recalled their satisfaction at their follow-up visit (1wk, 1, and 3mo after the application of BoNT/A). Patients with a rating of 1-3 were classified as not

Table 1 BEB assessments at baseline and follow-up visit mean±SEM

Assessments	Baseline (*n*=61)	Follow-up visit (*n*=61)		
		1wk	1mo	3mo
JRS score	5.97±0.19	2.67±0.22[a]	1.62±0.17[a]	2.13±0.80[a]
BSDI score	2.50±0.15	1.36±0.11[a]	0.66±0.08[a]	0.49±0.07[a]
Changes in JRS		3.31±0.23	4.36±0.21	3.85±0.21
Changes in BSDI		1.19±0.13	1.89±0.14	2.06±0.15

BEB: Benign essential blepharospasm; JRS: Jankovic Rating Scale; BSDI: Blepharospasm Disability Index; SEM: Standard error of measurement. [a]*P*<0.0001 *vs* baseline.

at all satisfied, those with a rating of 4-7 as somewhat satisfied, and those with a rating of 8-10 as very satisfied.

Statistical Analysis Wilcoxon signed rank tests were used to assess changes in measures of depression/anxiety/sleep disorder and in BEB measures from follow-up to baseline. Results from one investigator were reported in this study as the mean and standard error of mean for all eyes. Furthermore, Spearman correlations between the measures of depression/anxiety/sleep disorder of patients and the BEB measures were calculated. All statistical analyses were performed using the Statistical Package for the Social Science, Version 20.0 (SPSS Inc., Chicago, IL, USA). A *P*-value of <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics Sixty-one subjects were enrolled in the study with a mean age of 61.05±5.51. Forty-five (73.8%) were female participants. Eleven patients (18.1%) had a previous clinical diagnosis of depression and were on antidepressant medications, 4 patients (6.6%) had a previous clinical diagnosis of anxiety, and 3 patients (4.9%) were on antianxiety therapy.

At the initial visit, the mean JRS score was 5.97±0.19, the BSDI score was 2.50±0.15 (Table 1). The baseline average GAD-7 score was 7.78±0.57, with 15 patients having a score greater than 10; the average PHQ-8 score was 8.12±0.58, with 14 patients having a score greater than 10. The initial average AIS score was 7.62±0.66 (Figure 1).

Comparison Between Baseline and Follow-Up Sixty-one patients returned for follow-up at 1wk, 1, and 3mo after the BoNT/A injection treatment. At 1wk of follow-up, the average JRS score, BSDI, PHQ-8, and GAD-7 improved significantly to 2.67±0.22, 1.36±0.11, 4.43±0.31 and 4.20±0.36 (*P*<0.0001), respectively, compared to the initial visit, while the average AIS did not improve (*P*>0.05). At 1mo follow-up, the mean JRS, BSDI, PHQ-8 and GAD-7 score significantly improved to 1.62±0.17, 0.66±0.08, 2.26±0.17 and 2.58±0.21 (*P*<0.0001), respectively, the mean AIS score improved to 4.67±0.54 (*P*<0.001); At 3mo of follow-up, the average JRS score, BSDI, PHQ-8 and GAD-7 AIS score were 2.13±0.80, 0.49±0.07, 2.41±0.16, and 1.95±0.14 (*P*<0.0001), respectively,

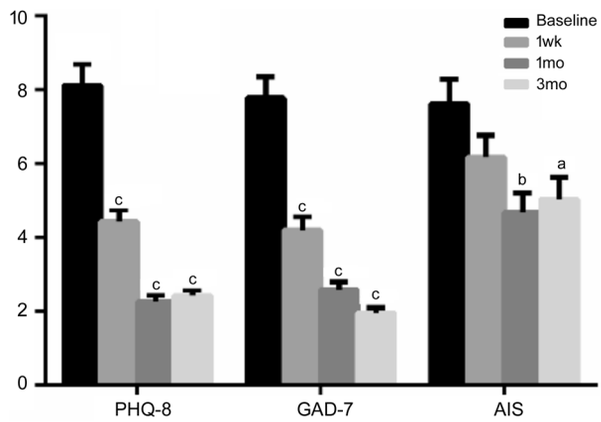

Figure 1 Comparison between baseline and follow-up scores of depression (PHQ-8), anxiety (GAD-7) and sleep disorder (AIS) scores Patients were treated with BoNT/A with for their BEB during this interval. All the scores were significantly improved in the 1wk, 1, 3mo follow-up periods. BEB: Benign essential blepharospasm; BoNT/A: Botulinum toxin type A; PHQ-8: Questionnaire Depression Scale; GAD-7: Generalized Anxiety Disorder 7 item scale; AIS: Athens insomnia scale. [a]*P*<0.01, [b]*P*<0.001, [c]*P*<0.0001 *vs* controls.

the average AIS score improved to 5.03±0.59, compared to the initial visit (*P*<0.01; Table 1, Figure 1).

The average changes in JRS were 3.31±0.23, 4.36±0.21, 3.85±0.21 and the average changes in BSDI were 1.19±0.13, 1.89±0.14, 2.06±0.15 in the 1wk, 1, and 3mo follow-up visit (Table 1).

Correlation Between Change in BEB Symptoms and Depression/Anxiety/Sleep Disorders At baseline, worse BSDI scores were correlated with worse GAD-7 (spearman correlation coefficient *r*=0.709, *P*<0.001) and PHQ-8 (*r*=0.411, *P*=0.001), but not with worse AIS (*r*=0.013, *P*=0.389). At 1mo follow-up visit, there is no correlation between change in BSDI and change in PHQ-8 (*r*=0.197, *P*=0.13), as well as change in AIS (*r*=0.045, *P*=0.73), the change in GAD-7 did show a mild association with change in BSDI (*r*=0.37, *P*=0.04; Figure 2).

Subgroup analysis was performed in patients with other chronic or ophthalmic diseases known to be related to depression/anxiety/sleep disorders, patients clinically diagnosed with depression or anxiety, and patients without diagnosed with anxiety or depression. Change in BSDI did correlate with

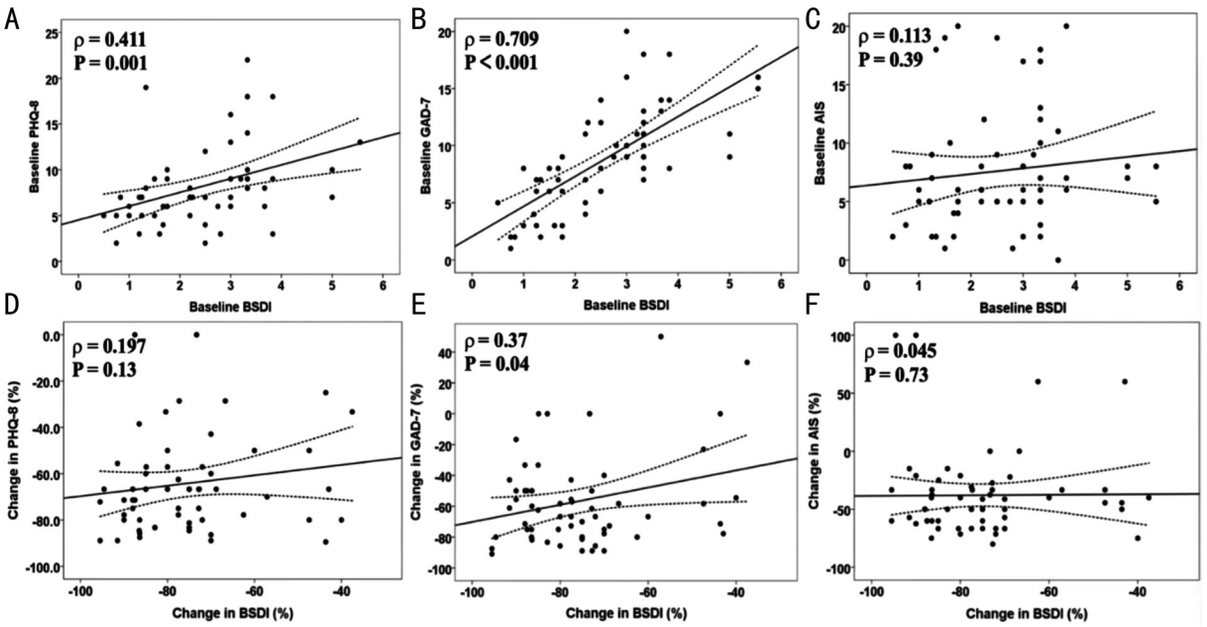

Figure 2 Correlation between change in BEB symptoms and depression/anxiety/sleep disorders A-C: Correlation between baseline BSDI and baseline PHQ-8/GAD-7/AIS score. D-F: Correlation between the change in BSDI and the change in the PHQ-8/GAD-7/AIS score at 1mo of BoNT/A treatment follow-up. The Spearman rank correlation coefficients (*r* value) are shown with statistical significance of the correlations. The linear regression line is shown with the 95% confidence intervals of the mean. BEB: Benign essential blepharospasm; BSDI: Blepharospasm Disability Index; BoNT/A: Botulinum toxin type A; PHQ-8: Questionnaire Depression Scale; GAD-7: Generalized Anxiety Disorder 7 item scale; AIS: Athens insomnia scale.

Table 2 BSDI scores at baseline and follow-up in the group of patients without prior diagnosis of depression or anxiety compared to the group of patients with a prior diagnosis of depression or anxiety mean±SEM

Characteristics	BSDI		
	Baseline	1mo follow-up	*P*
Patients without the diagnosis of depression or anxiety (*n*=46)	2.23±0.13	0.62±0.04	<0.0001
Patients with the diagnosis of depression or anxiety (*n*=15)	2.64±0.21	0.75±0.17	<0.0001

BSDI: Blepharospasm Disability Index; SEM: Standard error of measurement.

Table 3 Correlation between change in BEB symptoms and change in depression/anxiety/sleep disorder symptoms in specific subgroups

Assessments	BSDI[a]		
	Patients without depression or anxiety (*n*=38)	Patients with depression or anxiety (*n*=15)	Patients with comorbidities other than depression and anxiety (*n*=8)
dPHQ-8[b]	*r*=0.369, *P*=0.025	*r*=0.354, *P*=0.195	*r*=0.926, *P*=0.001
dGAD-7[c]	*r*=0.37, *P*=0.024	*r*=0.044, *P*=0.86	*r*=0.379, *P*=0.354
dAIS[d]	*r*=0.13, *P*=0.439	*r*=0.249, *P*=0.369	*r*=0.251, *P*=0.548

[a]Difference between BSDI at 1mo follow-up and at baseline; [b]Difference between PHQ-8 at 1mo of follow-up and at baseline; [c]Difference between GAD-7 at 1mo follow-up and at baseline; [d]Difference between AIS at 1mo of of follow-up and at baseline; BEB: Benign essential blepharospasm; BSDI: Blepharospasm Disability Index; PHQ-8: Questionnaire Depression Scale; GAD-7: Generalized Anxiety Disorder 7 item scale; AIS: Athens insomnia scale.

change in PHQ-8 and GAD-7 in the subgroup of patients who were without a prior diagnosis of anxiety or depression (*n*=38, *r*=0.369, *P*=0.025; *r*=0.37, *P*=0.024), and change in BSDI did correlate with change in PHQ-8 in the subgroup with ocular and systemic comorbidities (*n*=8, r=0.926, *P*=0.001). No correlation was found in patients with a prior diagnosis of depression or anxiety (*n*=15, *r*=0.354, *P*=0.195; *r*=0.044, *P*=0.86), however, their BSDI scores improved after treatment similar to the scores of patients without prior depression or anxiety (Table 2). There was no correlation between the change in BEB symptoms and the change in the AIS score in three subgroups (Table 3).

Treatment Satisfaction At the time of the 1wk follow-up visit, 98.3% of the subjects (60/61) were at least somewhat satisfied with BoNT/A treatment for BEB with a mean satisfaction score was 7.8±1.3. At the time of the 1mo follow-up visit, 96.7% of the subjects (59/61) were at least somewhat satisfied and the satisfaction score was 8.5±1.3, while at the

Table 4 Satisfaction with BoNT/A treatment

Treatment satisfaction	Follow-up visit		
	1wk (*n*=61)	1mo (*n*=61)	3mo (*n*=61)
Very satisfied (NRS 8-10), *n* (%)	39 (63.9)	51 (83.6)	41 (67.2)
Somewhat satisfied (NRS 4-7), *n* (%)	21 (34.4)	8 (13.1)	16 (26.2)
Not at all satisfied (NRS 1-3), *n* (%)	1 (1.6)	2 (3.3)	4 (6.6)
Mean (SD) satisfaction score	7.8 (1.3)	8.5 (1.3)	7.6 (1.8)

Subjects were asked "How satisfied are you at the moment with the current effect of your medication?". NRS: Numerical rating scale; SD: Standard deviation; BoNT/A: Botulinum toxin type A.

time of the 3mo follow-up visit, 93.4% of the subjects (57/61) were at least somewhat satisfied and the satisfaction score was 7.6±1.8 (Table 4). However, the proportion of very satisfied patients reached the highest at 1mo of follow-up (83.6%, 51/61).

DISCUSSION

BEB can cause a serious psychological burden on patients. Although it is not a life-threatening disease, it has a great potential impact on the quality of life. Blinking and spastic eyelid closure seriously affect patients' daily life activities, such as reading, driving, walking or interpersonal communication. This impact on daily life can lead to career failure, social withdrawal and depression[13].

Treatment with BoNT/A injections temporarily reduces symptoms of BEB, is well tolerated, and can improve quality of life[14]. Our study showed that the severity of BEB symptoms was positively correlated with the severity of depression/anxiety. During the follow-up period of BoNT/A treatment, BEB symptoms and the severity of depression/anxiety improved significantly. We chose the GAD-7 and PHQ-8 questionnaires because they are simple questionnaires that can be self-administered and easily incorporated into busy clinical practice. In addition, these questionnaires can also grade the severity of symptoms. The JRS and BSDI provide appropriate efficacy measurement standards in clinical trials of patients with BEB, and the change of 2 points of JRS and 0.7 points of BSDI are clinically meaningful[15]. In our study, the average change in JRS and BSDI have both clinically significant in the follow-up visit, indicating that BoNT/A can significantly improve motor and non-motor symptoms of BEB. In recent years, sleep disorders have become a major social problem of concern all over the world[16]. Sleep quality is crucial for physical and mental health, and sleep dysfunction directly affects autonomic nervous and endocrine functions, leading to extensive changes in many aspects of the body system[17]. The AIS is a very useful tool in both clinical and research settings, except for when assessing severity. Previous studies have shown that sleep dysfunction is associated with ocular surface diseases such as dry eye[18]. However, little is known about its relationship with the BEB. We found that after BoNT/A injection, the symptoms of sleep disorder improved, but there is no positive correlation between the severity of BEB symptoms and the severity of sleep disorder. Interestingly, many patients expressed that the improvement of sleep can conversely promote the relief of BEB symptoms.

The correlation between a change in BEB symptoms and the change in PHQ-8/AIS surveys were not statistically significant except the change in GAD-7 did show a mild association with change in BSDI at 1mo follow-up visit. This may be due to the relief of BEB symptoms was obvious, while the relief of depression/anxiety/sleep disorders varies greatly among individuals after the BoNT/A treatment. To further investigate the association between BEB and depression, anxiety and sleep disorder, subgroup analysis were performed. The results reveal that patients without prior diagnosis or treatment of depression/anxiety had a strong correlation between a change in their BEB symptoms and a change in their levels of anxiety and depression. This may be due to their psychological symptoms being related to the inconvenience in life caused by BEB and that their anxiety and depression improved with relief from the symptoms of BEB. Patients with comorbidities associated with depression and anxiety also show a strong positive correlation between changes in their BEB symptoms and changes in their depression levels which benefitted from our BoNT/A treatment intervention. Another study showed that the treatment of physical conditions improved the depression and anxiety symptoms associated with chronic obstructive pulmonary disease patients[19]. On the other hand, patients with previous clinical diagnosis of depression or anxiety did not show a similar correlation, although their BSDI scores were similar to those of patients without previous diagnosis of depression or anxiety. This may be related to the more serious GAD-7 and PHQ-8 scores of the previous group at baseline or to some pathological basis for their depression/anxiety symptoms.

Patient satisfaction with BoNT/A treatment regimens for BEB was high. One week after injection, the proportion of patient with very satisfied was the lowest, the low satisfaction was associated with stiff facial expression, incomplete closure of eyelid fissure, dry eyes and tears in the early stage of BoNT/A injection. Three months after follow-up, Low satisfaction

may be related to the recurrence of symptoms in some patients. Therefore, when the effect of the treatment reached its peak, the satisfaction with the BoNT/A treatment was the highest, but in the interview before reinjection, the satisfaction decreased. It is worth noting that the retrospective BSDI and JRS evaluation showed that even at the time of peak effect, some subjects still considered themselves had obvious symptoms. However, BEB is a chronic disease with repeated symptoms. Therefore, when the treatment cycle is approaching its end, the functional impairment and disability caused by BEB (for example, difficulties in daily activities such as driving and reading) worsen, and patient satisfaction decreases.

The mechanisms of the relationship between BEB and depression and anxiety are still unclear. An important question is whether non-motor symptoms are secondary symptoms of motor symptoms or part of the clinical spectrum of BEB. However, emotional problems aggravate facial symptoms[20]. Several studies have shown that patients with dyskinesias, such as Parkinson's disease, are generally accompanied by depression or other mental disorders[21]. From the perspective of pathophysiology, the functional connections of basal ganglia, cerebellum, primary/secondary sensorimotor cortex and visual areas in patients with BEB have changed[21-22]. The connections between the basal ganglia and the auxiliary motor area[23], and between the sensorimotor cortex, the auxiliary motor area, the precuneus, the premotor cortex, the parietal cortex, and the parietal cortex also changed[24]. This extensive abnormal connection could explain the extensive damage of multiple motor and non-motor domains in BEB[25]. Recent studies have also shown that facial injection of BoNT/A can treat depression by interrupting proprioceptive feedback from the face to the brain, which can strengthen and maintain negative emotions expressed by the corresponding simulated muscles[22,26]. However, despite the clinical observations, there was a noted lack of biomarker-related assessments. Stark *et al*[27] recently published a task-based fMRI study showing that BONT/A injections and inhibition of frowning alter the processing of emotional faces in the amygdala; these findings were confirmed in 10 healthy females. Future studies should focus on exploring the mechanistic underlying the BONT/A effect at the neurobiological level.

Due to the small sample size, the absence of a control group, and confounding factors, our study has some limitations. To address the limitations of confounding factors, we performed subgroup analysis and multivariable analysis to try to isolate some confounding factors, such as the presence of comorbidity, including depression/anxiety. It is worth noting that all subjects are Chinese and most participants are women, so our results may not be extended to other races and genders. Our findings need to be confirmed in larger controlled clinical trials. Finally, this is a single-center study, which can make our results vulnerable to hospital bias.

To our knowledge, this survey is the most comprehensive study investigating patients' psychological diseases and the symptoms improvement with BoNT/A treatment for BEB to date. The survey revealed that, overall, patient satisfaction with BoNT/A treatment regimens for blepharospasm was very high, and BoNT/A can significantly improve motor and non-motor symptoms of BEB. Despite methodological limitations, the results of this study emphasize the effectiveness of BoNT/A in the treatment of depression and therefore pave the way for its use in the field of psychiatry. However, further research is needed to confirm these findings and understand the underlying mechanisms.

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REFERENCES

1 Titi-Lartey OA, Patel BC: Benign Essential Blepharospasm. In: *StatPearls.* edn. Treasure Island (FL); 2023.

2 Simpson DM, Blitzer A, Brashear A, Comella C, Dubinsky R, Hallett M, Jankovic J, Karp B, Ludlow CL, Miyasaki JM, Naumann M, So Y, Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: Botulinum neurotoxin for the treatment of movement disorders (an evidence-based review):report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2008;70(19):1699-1706.

3 Hallett M. Blepharospasm. *Neurology* 2002;59(9):1306-1312.

4 Duarte GS, Rodrigues FB, Marques RE, Castelão M, Ferreira J, Sampaio C, Moore AP, Costa J. Botulinum toxin type A therapy for blepharospasm. *Cochrane Database Syst Rev* 2020;11(11): CD004900.

5 Albanese A, Sorbo FD, Comella C, Jinnah HA, Mink JW, Post B, Vidailhet M, Volkmann J, Warner TT, Leentjens AF, Martinez-Martin P, Stebbins GT, Goetz CG, Schrag A. Dystonia rating scales: critique and recommendations. *Mov Disord* 2013;28(7):874-883.

6 Bitar MS, Olson DJ, Li MB, Davis RM. The correlation between dry eyes, anxiety and depression: the sicca, anxiety and depression study. *Cornea* 2019;38(6):684-689.

7 Choi KW, Kim YK, Jeon HJ. Comorbid anxiety and depression: clinical and conceptual consideration and transdiagnostic treatment. *Adv Exp Med Biol* 2020;1191:219-235.

8 Kilic-Berkmen G, Kim H, Chen DD, Yeo CI, Dinasarapu AR, Scorr LM, Yeo WH, Peterson DA, Williams H, Ruby A, Mills R, Jinnah HA. An exploratory, randomized, double-blind clinical trial of dipraglurant for blepharospasm. *Mov Disord* 2024;39(4):738-745.

9 Fu S, Yang Z, He X, Liu D, Yang Z, Zhang J, Du L. Long-term efficacy of bilateral globus pallidus stimulation in the treatment of meige syndrome. *Neuromodulation* 2024:S1094-7159(24)00058-8.

10 Yin B, Peng B, Luo Y, Fan SH, Xiao T, Zou XL, Dong HJ. Efficacy of repetitive transcranial magnetic stimulation combined with botulinum toxin type A for benign essential blepharospasm patients accompanied by anxiety and depression. *Neuropsychiatr Dis Treat* 2021;17:2707-2711.

11 Gaćina K, Lešin M, Sarajčev D, Rotim N. The effect of botulinum toxin type a in patients with essential blepharospasm. *Acta Clin Croat* 2022;61(3):379-385.

12 Kroenke K, Spitzer RL, Williams JB, Monahan PO, Löwe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Ann Intern Med* 2007;146(5):317-325.

13 Müller J, Kiechl S, Wenning GK, Seppi K, Willeit J, Gasperi A, Wissel J, Gasser T, Poewe W. The prevalence of primary dystonia in the general community. *Neurology* 2002;59(6):941-943.

14 Fang XB, Xie MS, Song ZB, Zhong ZG, Wang Y, Ou ZL, Dang C, Li L, Zhang WX. Long-term treatment of blepharospasm with botulinum toxin A: a service-based study over a 16-year follow-up in Southern China. *Neurol Sci* 2020;41(3):645-652.

15 Jankovic J, Kenney C, Grafe S, Goertelmeyer R, Comes G. Relationship between various clinical outcome assessments in patients with blepharospasm. *Mov Disord* 2009;24(3):407-413.

16 Kerkhof GA. Epidemiology of sleep and sleep disorders in The Netherlands. *Sleep Med* 2017;30:229-239.

17 Gozal D, Dumin M, Koren D. Role of sleep quality in the metabolic syndrome. *Diabetes Metab Syndr Obes Targets Ther* 2016;9:281-310.

18 Yu XN, Guo HL, Liu X, Wang GW, Min Y, Chen SS, Han SS, Chang RT, Zhao XY, Hsing A, Zhu SK, Yao K. Dry eye and sleep quality: a large community-based study in Hangzhou. *Sleep* 2019;42(11):zsz160.

19 Panagioti M, Scott C, Blakemore A, Coventry PA. Overview of the prevalence, impact, and management of depression and anxiety in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2014;9:1289-1306.

20 Wollmer MA, Magid M, Kruger THC, Finzi E. Treatment of depression with botulinum toxin. *Toxins* 2022;14(6):383.

21 Burn DJ. Beyond the iron mask: Towards better recognition and treatment of depression associated with Parkinson's disease. *Mov Disord* 2002;17(3):445-454.

22 Schulze J, Neumann I, Magid M, Finzi E, Sinke C, Wollmer MA, Krüger THC. Botulinum toxin for the management of depression: an updated review of the evidence and meta-analysis. *J Psychiatr Res* 2021;135:332-340.

23 Ni MF, Huang XF, Miao YW, Liang ZH. Resting state fMRI observations of baseline brain functional activities and connectivities in primary blepharospasm. *Neurosci Lett* 2017;660:22-28.

24 Huang XF, Zhu MR, Shan P, Pei CH, Liang ZH, Zhou HL, Ni MF, Miao YW, Xu GQ, Zhang BW, Luo YY. Multiple neural networks malfunction in primary blepharospasm: an independent components analysis. *Front Hum Neurosci* 2017;11:235.

25 Graff-Radford J, Williams L, Jones DT, Benarroch EE. Caudate nucleus as a component of networks controlling behavior. *Neurology* 2017;89(21):2192-2197.

26 Demchenko I, Swiderski A, Liu H, Jung H, Lou W, Bhat V. Botulinum toxin injections for psychiatric disorders: a systematic review of the clinical trial landscape. *Toxins* 2024;16(4):191.

27 Stark S, Stark C, Wong B, Brin MF. Modulation of amygdala activity for emotional faces due to botulinum toxin type A injections that prevent frowning. *Sci Rep* 2023;13(1):3333.