Comorbidity between chronic headache and depression treated with botulinum toxin: literature review

A comorbidade entre cefaleia crônica e depressão tratada com toxina botulínica: revisão da literatura

Denis Eduardo Bertini Bo[1], Eduardo de Melo Carvalho Rocha[1]

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ABSTRACT

BACKGROUND AND OBJECTIVES: It is estimated that up to 40% of patients with migraine have at least one episode of major depression during their lifetime. On the other hand, patients with depression are twice as likely to suffer from migraine when compared to the population without the mood disorder. The comorbidity of both conditions increases the frequency of pain crises and the individual's disability. A therapy that could act on the disorders, when simultaneous, would offer advantages through a broader and more effective action, such as botulinum toxin (BTX). Due to the lack of a clear definition on the subject, the objective of this study was to review how the concomitant treatment with BTX of the two morbidities behaves.

CONTENTS: A review of articles in English, Portuguese, and Spanish indexed in Pubmed/Medline, LILACS and Scielo databases was carried out. Of the eight articles selected, most individuals were women aged 40 to 50 years. The sample size ranged from 30 to 715 subjects. The predominance was of prospective studies. All studies found a significant reduction in pain. Six studies found a significant decrease in depression. The frequency of adverse effects ranged from 4.1% to 30%, with eyelid ptosis and headache being the most frequent.

CONCLUSION: BTX seems to be useful for the treatment of chronic headache and depression. There was a tendency to relate the improvement in depression with the decrease in pain. The specific action of the toxin in the treatment of depression was inconclusive. New studies, with high methodological rigor, as well as systematic reviews, should be carried out to reach a greater depth of comprehension of the subject and to determine the real efficacy of BTX in relieving concomitant headache and depression.

Keywords: Depression, Botulinum toxins type A, Disorder headache.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Estima-se que até 40% dos pacientes com migrânea apresentam, pelo menos, um episódio de depressão maior ao longo da vida. Por outro lado, pacientes com depressão apresentam duas vezes mais chance de ter migrânea quando comparados à população sem transtorno de humor. A comorbidade dos dois quadros aumenta a frequência das crises de dor e a incapacidade do indivíduo. Uma terapêutica que pudesse agir nos transtornos, quando simultâneos, ofereceria vantagens, por uma ação mais ampla e eficaz, a exemplo da toxina botulínica (TXB). Por faltar ainda uma clara definição sobre o tema, o objetivo deste estudo foi revisar como se comporta o tratamento concomitante das duas morbidades com a TXB.

CONTEÚDO: Foi realizada revisão de artigos indexados nas bases de dados Pubmed/Medline, LILACS, Scielo nos idiomas inglês, português e espanhol. Dos oito artigos selecionados, a maioria dos indivíduos foram mulheres de 40 a 50 anos. O tamanho das amostras variou de 30 a 715 pacientes. A predominância foi de estudos prospectivos. Todos os estudos encontraram redução significativa da dor. Seis trabalhos encontraram diminuição significativa da depressão. A frequência dos efeitos adversos variou de 4,1% a 30%, sendo ptose palpebral e dor de cabeça os mais frequentes.

CONCLUSÃO: A TXB parece ser útil para tratamento da cefaleia crônica e depressão. Houve uma tendência a relacionar a melhora da depressão com a diminuição da dor. A ação específica da toxina no tratamento da depressão foi inconclusiva. Novos estudos, com alto rigor metodológico, assim como revisões sistemáticas, devem ser realizados para alcançar maior aprofundamento do assunto, a fim de determinar a real eficácia da TXB no alívio da cefaleia e depressão concomitantes.

Descritores: Depressão, Toxina botulínica tipo A, Transtornos de enxaqueca

INTRODUCTION

The term cephalalgia encompasses all existing headaches. It is estimated that more than 90% of the population has some type of headache throughout their lives[1]. It can be manifested as chronic pain and substantially interfere with quality of life and ability to work[2]. According to the World Health Organization (WHO)[3], headaches are among the 10 most disabling conditions for both genders, although they are among the five worst for women, because they are the most frequently affected by the disorder[1].

Denis Eduardo Bertini Bo – https://orcid.org/0000-0001-8821-748X;
Eduardo de Melo Carvalho Rocha – https://orcid.org/0000-0003-2078-5450.

1. Federal University of São Carlos, Gerontology Department, São Carlos, SP, Brazil.

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Correspondence to:
Denis Eduardo Bertini Bo
E-mail: denis_edu_bo@yahoo.com.br

Primary headaches are understood as the disease itself, without a clear underlying cause, such as a tumor, infection, or trauma[4]. Among the primary headaches, the most prevalent are migraine and tension-type headache. In Brazil, the occurrence of migraine is around 15.8%, while tension-type headaches may reach 22.9%. However, migraine causes a strong impact on the individual's quality of life, which motivates him/her to seek treatment[1].

The association between chronic pain and mental disorders, especially depression, has been reported in the literature[5,6]. In some reviews, the concomitant occurrence between pain and depression ranges between 30% and 60%[7,8]. In an article analyzing 1000 patients of a specific health plan, those with at least one pain condition had more depression and anxiety than individuals without pain[9]. In hospitalized patients, this association becomes even more evident[10].

In the case of headaches, the strong relationship with depression is also stated by other authors. The two conditions, when concomitant, cause an increase in the frequency of pain crises, as well as a greater patient disability. This connection seems to be bidirectional. It is estimated that up to 40% of patients with migraine have at least one episode of major depression in their lifetime. In addition, migraine patients have a three times higher risk of developing depression than the general population. On the other hand, patients with depression are twice as likely to develop migraine when compared to the population without the mood disorder[1,11-15].

The present study's objective was to expose, in some level of detail, the pathophysiology of the association between migraine and major depression as an example and as an illustration of how the connection between headaches and psychiatric mood disorders is comprehended. The reasoning being that the mechanisms of the comorbidity between migraine and major depression are clearer.

The condition called major depression (whose prevalence in the population may reach 17% throughout life)[16] is constituted, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[17], by the following criteria, as shown in table 1.

Table 1. Diagnostic criteria for major depressive episode

At least 5 symptoms, present for at least 2 weeks, on most days:
One symptom must necessarily be: Depressed mood; Marked decrease in interest or pleasure in most or all activities.
Other symptoms: Weight loss unrelated to dieting, significant weight gain, or appetite changes; Hypersomnia or insomnia; Psychomotor agitation or depression; Fatigue or feeling of loss of energy; Feeling of worthlessness or excessive or inappropriate guilt; Indecisiveness or difficulty concentrating or reasoning; Recurrent thoughts of death or suicidal ideation (with or without planning).
Symptoms that cause significant impact in various spheres, such as social or work-related.
Symptoms that are not due to substance/drug use or other illness.
Symptoms not explained by schizoaffective or psychotic disorder, and no presence of hypomanic or manic episode.

Source: DSM-5[17].

Migraine is often accompanied by photophobia and/or vomiting; it is very intense, unilateral, and pulsatile. The crisis can last up to 72 hours if not treated properly[18].

Several elements are involved when it emerges, as well as in its chronification, which are genetic, hormonal, inflammatory, environmental, dietary, related to sleep, psychological, and psychiatric[1,19,20]. All these elements, in some way, have an intersection with the mechanisms that generate depression.

From the genetic angle, research also reaffirm the strong link between major depression and migraine. A recent study showed a greater association (by analyzing the whole genome) of migraine with psychiatric disorders when compared to other neurological disorders[21]. Both migraine and depression have about 20% of their variability attributed to shared genes, as suggested by a study with twins[22,23]. In addition, a polymorphism in the serotonin transporter gene has been associated with migraine as well as depression[24]. Alterations through DNA methylation in the corticotropin-releasing factor in the hypothalamic-pituitary-adrenal (HPA) axis points to a hypersensitivity to pain caused by stress[25]. Psychosocial stress, in turn, is pointed out as an important influencing factor for both depression and migraine[26,27].

It is known that the reaction to stress, initially, is a healthy response of the body. Challenging and frightening situations require mobilizing action from human beings. The reaction to stress can provide a more active, vigorous, and productive behavior. However, in excess and/or when it is prolonged, it can cause damage[28,29]. In moments of threat, the sympathetic autonomic nervous system and the HPA axis are activated, which generates catecholamine release (mainly adrenaline) and cortisol secretion by the adrenal gland.

When the stressful situation ceases, these substances return to their initial stage. But if it persists, the stress hormones lead to an overload of the organism with cardiovascular consequences, bone density alteration, weight loss, amenorrhea, and alteration in the regulation of future responses to stress, anxiety, and depression[30]. The modification in the responsiveness of the HPA axis results in a mismatch in cortisol secretion, influencing inflammatory reactions. Among other consequences, there is an increase in cytokines, facilitating the development of autoimmune and inflammatory diseases[26] that can develop with pain.

The increased activity of the HPA axis can also induce functional changes in neurons and consequent neuronal death, accompanied by structural changes in the cerebral cortex, such as atrophy or decrease in its volume. Such a situation can have consequences on behavior, including mood worsening. A significant portion of depressed patients present evident increased activity of the HPA axis: 20% to 40% of those seen in outpatient clinics and 40% to 60% of hospitalized patients[16].

In fact, from the neurofunctional viewpoint, brain structures are pointed out as acting in common in pain and depression. The anterior cingulate cortex, the thalamus, the amygdala, the periaqueductal gray matter, in addition to areas that initially would not be related to pain processing, such as the parahippocampal and fusiform gyrus, retrosplenal cortex, posterior cingulate cortex, and striatum, seem to be involved sometimes in the experience of pain itself; sometimes in its emotional components,

contributing to its chronification; and sometimes in the very emergence of the depressive disorder[31,32].

Furthermore, it must be mentioned that some of these structures, such as the periaqueductal gray matter, together with the hypothalamus, the raphe nuclei, and the *locus coeruleus*, compose a central pain modulation system, of which serotonin and norepinephrine are the main neurotransmitters. This system can inhibit or amplify nociceptive signals from the periphery. Dysregulation of such neurotransmitters has been used to explain depression and may contribute to the onset of pain/migraine symptoms concomitant with the mental disorder[33-35].

On the other hand, it is important to remember inflammatory factors already described in the etiology of migraine and depression. Not only tissue injury and/or an infection can release pro-inflammatory cytokines. Chronic cortisol dysregulation, for example, can also induce them (as already seen). These cytokines can cross the hematoencephalic barrier and act in the brain[36]. Observations of the appearance of depressive symptoms in patients treated with cytokines such as interferon have shown the connection between inflammation and depression. Pain is a form of tissue response that promotes defense behavioral reactions. However, when pain becomes chronic, unrelated to tissue injury itself, it becomes a problem. Likewise, when depressive symptoms persist, despite the absence of a clear cause or grief, they are considered pathological[25].

A still very controversial aspect of the association between migraine and psychiatric/psychological symptoms is the possibility that there are specific personality characteristics of those who suffer from migraine. One of the earliest works in this line[37] talks about the "migraine personality", which would be composed of traits of rigidity, compulsiveness, perfectionism, ambition, competitiveness, chronic resentment, and centralization of tasks due to the impossibility of delegating them.

Currently, studies suggest that patients with migraine would present traits of the DSM5[17] avoidant personality disorder. They would be excessively worried, fearful, insecure people, with high sensitivity to stress, and therefore prone to develop anxiety and depression. However, there are still doubts if such traits would be responsible for the association between migraine and depression[1].

The fact is that the comorbidity between the two conditions, headache (migraine in particular) and depression, is frequent. Therefore, a therapeutic strategy that could act on both disorders, when they occur simultaneously, could offer advantages through a broader and more effective action, such as the botulinum toxin (BTX).

BTX is an agent produced from the fermentation of *Clostridium botulinum*, a gram-positive anaerobic bacteria in spore form, common in soil and in marine environments[38]. Eight immunologically distinct serotypes are identified in its composition. Of these, seven are neurotoxins (A, B, C1, D, E, F, G)[39]. Their action consists of inhibiting the release of acetylcholine in the synaptic cleft, and BTX-A is the most studied and applied in clinical practice.

To exert its effect, BTX, since it has a high affinity for cholinergic synapses, penetrates the motor neuron that innervates the skeletal muscles. Inside the cytoplasm, it binds specifically to the SNARE protein complex. Similar to enzymes, the toxin cleaves the peptide bonds of the SNARE proteins[39]. As a result, the synaptic vesicle is not anchored to the inner surface of the cell membrane, blocking vesicle fusion, a necessary condition for the release of acetylcholine. Then, a flaccid paralysis in the affected muscle fibers occurs (chemical denervation)[40].

The action of BTX happens in two to five days on average and can last for up to six months (usually about four months). The restoration of physiology usually happens through two known mechanisms. The first occurs through the formation of new axonal sprouts with the formation of new smaller end plates, leading to temporary reinnervation. The second comes from the regeneration of the SNARE complex proteins, allowing the return of the coupling of acetylcholine vesicles on the inner side of the neuronal membrane[41].

The contribution of BTX in the treatment of headaches results (although it is not definitively confirmed) from the relaxation of the muscles affected by the substance. A relation with decrease in pressure on the trigeminal nerve roots is also suggested[42]. And, more recently, there is evidence that the toxin acts on the release of substances and neurotransmitters involved in inflammation and nociception[43].

In the case of depression, BTX also contributes to the improvement of dysphoric symptoms[44,45]. This action is based on the so-called facial feedback effect. The hypothesis proposes a bidirectional link between the emotion regulatory centers in the brain and the facial muscles[46]. It seems natural to conclude that our facial expressions are influenced by our emotional state, but the opposite is not so easy to accept. Nevertheless, researchers[47-49] have detected that, regardless of the reason, expressing a more serious or smiling face affects our emotions. In the first case, frowning by contracting the corrugator muscles in the glabellar region can lead to a more negativistic view. Otherwise, in the second case, contracting the zygomatic muscles to smile would provide more joy and optimism. Therefore, broadly speaking, evidence adds up in affirming a significant effect of facial muscles on mood.

Study[50] suggests a hypothesis of how this influence would take place, especially for depression. The same mechanism, according to the authors, would explain the antidepressant action of BTX. The activity of the muscles in the eyebrows area would act on the proprioception of the optic branch of the trigeminal nerve. From there, through the mesencephalic trigeminal nucleus, there would be activation of the ventromedial prefrontal cortex and the *locus coeruleus*, and from the latter to the amygdala (structures important for emotional regulation)[51]. As BTX is injected into the forehead in the glabellar region, paralyzing the corrugator muscle, the proprioceptive signal sent by the optic branch of the trigeminal nerve to the brain would be altered. As a result, there would be a change in mood.

The present study's objective was to observe if the improvement of depressive symptoms would enable pain relief. On the other hand, due to the bidirectional relationship between headache and depression, to observe if the improvement of pain would influence psychiatric symptoms. Some studies evaluate the treatment with BTX in patients with both conditions, but there is no clear definition on the subject.

CONTENTS

A review of articles indexed in the Pubmed/Medline, LILACS, Scielo databases in English, Portuguese and Spanish was performed. The following keywords were used for the search: botulinum toxin, headache, depression, migraine and their correlates in Portuguese and Spanish.

The search was performed from March to June 2020. There was no restriction regarding the date of publication of the articles. Initially, the search found 1893 papers. Of these, eight articles were selected because they discussed the action of BTX in the two morbidities: depression and headache.

The eight selected studies were analyzed according to the following data: sample size; predominant gender; mean age; percentage of depressive disorder in the baseline; type of study; method of evaluation of both headache and depression; use of oral drugs for the treatment of headache and depression concomitant to the use of BTX; adverse effects of BTX; results obtained with the use of the toxin in both depression and headache; and follow-up period. This information is shown in tables 2, 3, and 4.

All the selected studies allowed the use of oral drugs (antidepressants) to treat depression simultaneously with the use of the toxin.

The inclusion and exclusion criteria were heterogeneous among the studies, thus allowing several types of headache to be present in the composition of the samples. However, all worked with patients with chronic primary headache, according to the criteria of the Headache Classification Committee of the International Headache Society (ICHD-3)[52].

Other variables were evaluated in the studies, such as sleep, anxiety, stress and repercussions of pain on quality of life and work.

Table 2. Studies included in the review

Authors	Females (%)	Age (years) Mean ± standard deviation	Depression (% in the sample and severity)
Boudreau et al.[53]	87.5	42.4 (19-66)	4.17 (moderate)
Zhang et al.[54]	76.67	42.97 (±12.86)	36 (moderate to severe)
Aydinlar et al. [55]	87.9	39.3 (±10.2)	7.9 (severity not mentioned)
Guerzoni[56]	84	45.21 (±10.12)	-
Kollewe et al.[57]	92	45.6 (±10.8)	-
Blumenfeld et al.[58]	84.8	43.0 (±11.3)	74.5 (mild to moderate) 11.4 (moderate, because severe cases were excluded)
Maasumi et al.[59]	86.1	45.1 (±13.2)	-
Demiryurek et al.[60]	73	34.73 (±6.40)	-

- Unavailable data.

Table 3. Type of study, sample size, outcome assessment, concomitant oral drugs, follow-up period

Authors	Type of study	Sample size	Instrument used for pain assessment	Instrument used for depression assessment	Concomitant oral drug for headache	Follow-up period
Boudreau[53]	Prospective	32	VAS HIT-6MIDAS	PHQ-9 BDI-II	For at least 10 days each month	24 weeks
Zhang[54]	Prospective	30	VAS* Number of days/months with headache. Duration of migraine attack in hours.	HAM-D	No use of prophylactic drugs, only abortifacient drugs	72 weeks
Aydinlar[55]	Prospective	190	MIDAS	DASS-21†	Use of prophylactic and abortifacient drugs	48 weeks
Guerzoni[56]	Retrospective	90	SF-36 VAS HIT-6	ZUNG-D †	Use of prophylactic and abortifacient drugs	3 years
Kollewe[57]	Prospective	27	SF-36 MSQ	BDI	Use of prophylactic and abortifacient drugs	60 weeks
Blumenfe[58]	Prospective	715	Pain diary*	PHQ-9	Use of prophylactic and abortifacient drugs	108 weeks
Maasumi [59]	Retrospective	359	HIT-6	PHQ-9	Use of oral drugs was not mentioned	1 year
Demiryurek[60]	Prospective	60	VAS MIDAS	BDI	Use of prophylactic and abortifacient drugs	12 weeks

VAS = Visual Analog Scale; HIT-6 = six-item Headache Impact Test; PHQ-9 = 9-item Patient Health Questionnaire; BDI = Beck Depression Inventory; DASS 21 = 21-item Depression, Anxiety, and Stress Scale; ZUNG-D = Zung's Self-rating Depression Scale; MIDAS = Migraine Disability Assessment Questionnaire; SF-36 = Short Form Health Survey; HAM-D = Hamilton Depression Rating Scale; MSQ = Migraine-specific quality of life questionnaire.
*: The test was applied, but results were not clear. †: not statistically significant.

Table 4. Adverse events reported in the studies

Area/system	Events	% in relation to the total of evaluated trials (8)
General	Syncope	12.5
	Flu-like symptoms	12.5
	Fainting during injection	12.5
Face	Forehead stiffness	12.5
	Eyelid ptosis	75
	Asymmetry in eyebrow position	12.5
	Facial palsy	12.5
Eyes	Diplopia	12.5
Local	Pain at the injection site	25
	Discomfort	12.5
	Erythema	12.5
	Edema	12.5
	Itching	12.5
	Hematoma	12.5
Neck	Lower neck	12.5
	Neck stiffness	12.5
	Neck pain	25
	Neck weight	12.5
	Neck sensibility	12.5
	Neck muscle weakness	12.5
Oropharyngeal	Chewing atony	12.5
	Dysphagia	25
	Sore throat	12.5
Gastrointestinal	Nausea	12.5
Nervous	Headache	62.5
	Migraine	12.5
Muscular	Weakness	37.5
	Myalgia	12.5
	Stiffness	25
Others	Shoulders sensitivity	12.5
	Skin tightening	12.5
	Pain (nonspecific)	12.5

DISCUSSION

As this is an innovative and unusual treatment proposal, a small number of articles on the subject is expected. Among the eight selected studies, seven used the PREEMPT[61] study as an application model for BTX injections, standardizing the experiments. The model recommends applying 155 IU of BTX in 31 areas of the head and neck, and there may be, depending on each case, an additional dose of 45 IU, going for other points, following a strategy called "follow the pain".

Only one study[54] did not follow the model mentioned above. In this case, applications were made using 5 to 10 IU of the BTX in each area, namely the frontal, temporal, glabellar, epicranial, aponeurosis, and occipital areas. The total dose ranged from 40 to 120 IU. Thus, smaller doses than those used in the other studies. However, it obtained a favorable response for decreased headache and improved mood symptoms. This study highlights the possibility of a lower dose of BTX for the treatment of headaches as well as depression.

Positive results for pain improvement were present equally in the other seven studies. However, some authors[55,56] did not observe improvement in depression, and they used less common scales for mood symptom assessment, such as DASS-21[55] and ZUNG-D[56] scales, unlike the other studies.

In one of these studies[55], the authors speculate that the improvement in depression may be more related to improved sleep than to the improvement of pain itself. In this study, sleep did not improve either, despite the diminishment of pain, allowing the authors to postulate about the possibility of a greater influence of sleep on the improvement or worsening of depression.

Author[56] recalls that the treatment of depression through BTX is still polemic and controversial. He justifies his position by arguing about authors who have obtained positive results and others who have not. It is still a relatively new technique, under development and with future potential for research, often leading to contradictory findings in studies.

In the present study, the described controversy also arose. Study[59] evaluated 359 patients using the HIT-6 scale for headache and the PHQ-9 scale for the other health aspects (including mood symptoms). Patients were allowed to use antidepressants. The HIT-6 scale detected 30.1% improvement of pain intensity and PHQ-9 detected 38% improvement for other health aspects. It was noteworthy that, of those who showed no reduction in pain on the HIT-6 scale (about 70%), 9.6% showed improvement on the PHQ-9. That is, approximately 10% of the patients in the sample improved in general health and mood, even though pain did not decrease. Nevertheless, after the appropriate statistical corrections, the study found that patients with reduced pain were 5.9 times more likely to have significantly improved depression. The authors then concluded that the improvement of depression in patients with chronic migraine treated with BTX was related to the improvement of pain.

One study[58] included 715 people with mild to moderate depressive disorder and observed improvement in depressive symptoms even in those patients with a small reduction in the frequency of days with headache, suggesting a positive effect on mood symptoms independent of the analgesic effects of the toxin.

In the remaining studies, the improvement of pain and depression occurred concomitantly, and it was not possible to state, as of the analysis of the results, that the improvement of depression was independent from that of pain by an action of the specific BTX antidepressant. Studies currently underway focus on the effect of BTX in resistant depression[62,63]. Such studies could bring more clarification on the subject.

All studies reported the presence of at least some type of adverse effect. Its frequency ranged from 4.1%[59] to 30%[53]. All the studies stressed the safety of the treatment. The adverse effects appeared with no severity and tended to disappear over time. Nonetheless, authors[58] pointed out that 3.5% of the evaluated patients abandoned the study due to some adverse effect.

The limitations were the restricted number of studies (only eight), which restricts the possibility of more robust conclusions with the intent of extending the treatment to clinical practice in general. The analyzed studies used samples with varied inclusion and exclusion criteria, grouping patients with different characteristics, making comparisons difficult. It's important to specially highlight the difficulty of comparing the various types of headaches in the different samples, in addition to the varied severity of symptoms in relation to headache and depression. The use of a drug concomitant to the treatment with BTX should also be remembered because this practice can influence the result, since, initially, it adds its effects to those of the toxin evaluated.

Only one study[53] limited the use of analgesic drugs. No studies used control or placebo groups, thus exposing an extremely important methodological bias. This bias prevents the elucidation of doubts about the phenomenon of spontaneous improvement and/or improvement caused by the action of some other element other than the specific drug (the toxin, in this case). However, for the present study, an integrative review, there was no concern to deepen the analysis of the quality of evidence.

On the other hand, there was almost total consensus in the manner of using the toxin, i.e., as described above, seven studies used the PREEMPT protocol as a model for toxin application, contributing to the comparative analysis. Finally, there is a language limitation, as the search focused on articles in English, Portuguese, and Spanish.

CONCLUSION

BTX seems to be useful for treating chronic headache and depression. However, there was a tendency to relate the improvement of depression with the decrease in pain. The specific action of the toxin in the treatment of depression was inconclusive. Due to the apparent positive potential, new clinical trial-type studies with high methodological rigor and systematic reviews should be carried out to determine the real efficacy of the treatment of BTX in the comorbidity between headache and depression. This study hopes, within its limitations, to have contributed to the elucidation of the subject.

AUTHORS' CONTRIBUTIONS

Denis Eduardo Bertini Bo
Data Collection, Writing - Preparation of the original
Eduardo de Melo Carvalho Rocha
Writing - Review and Editing, Supervision

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