

NATO KAKABADZE ^{1,2}, NERIMAN TSINTSADZE ^{1,2}, MIKHEIL ARTMELADZE ^{1,2},
ALBINA KADJAJA ³, MURAT TSINTSADZE ³, NINO TSINTSADZE ¹

IMPACT OF THE BOTULINUM NEUROTOXIN INJECTIONS ON PATIENTS WITH DEPRESSION: THERAPEUTIC MECHANISMS AND POSSIBLE FUTURE PERSPECTIVE

¹Avicenna - Batumi Medical University, Batumi, Georgia; ²“SoloMed” Clinic, Batumi, Georgia;

³Total Charm Vake, Tbilisi, Georgia

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ნატო კაკაბაძე ^{1,2}, ნერიმან ცინცაძე ^{1,2}, მიხეილ ართმელაძე ^{1,2},
ალბინა ქაჯაია ³, მურატ ცინცაძე ³, ნინო ცინცაძე ¹

ბოტულინის ნეიროტოქსინის ინექციების გავლენა დეპრესიის მქონე პაციენტებზე: თერაპიული მექანიზმები და შესაძლო მომავლის პერსპექტივა

¹ავიენა - ბათუმის სამედიცინო უნივერსიტეტი, ბათუმი, საქართველო; ²კლინიკა „სოლომედი“, ბათუმი, საქართველო; ³Total Charm ვაკე, თბილისი, საქართველო

რეზიუმე

მიუხედავად თანამედროვე მედიცინის მუდმივი, უწყვეტი განვითარებისა, დეპრესია კვლავ მნიშვნელოვან პრობლემად რჩება. არსებული მკურნალობის მეთოდები ხშირად არაეფექტურია, რის გამოც ხშირად მიმართავენ ექსპერიმენტულ მეთოდებს, ერთ-ერთ მათგანად გვევლინება - ბოტულინის ინექციები. ჩვენი მიზანი იყო შეგვეჯამებინა რა წინა კვლევები და გავგეხადა ის მისაწვდომი უფრო ფართო აუდიტორიისათვის, რათა კლინიკებს ჰქონდეთ წვდომა ამ ინფორმაციის არატრადიციულ შემთხვევებში გამოსაყენებლად. კვლევის მიზანი იყო არა უშუალოდ დეპრესიის განკურნება, არამედ ბოტულინის დადებითი ზემოქმედების შეფასება დეპრესიის მქონე პაციენტებზე. ჩვენი ყურადღება განსაკუთრებით მიიქცია იმ ფაქტმა, რომ ამ თემაზე კვლევა ჩვენს ქვეყანაში ჯერ არ ჩატარებულა. შეფასებისთვის, ჩვენი წინამორბედების მსგავსად, გამოყენებული იქნა ბეკის დეპრესიის ინვენტარის (BDI) კითხვარი, სულ 21 კითხვა, 15 მონაწილეს შორის ჩატარებულმა კვლევამ აჩვენა, რომ BoNT/A ინექციებმა მნიშვნელოვნად გააუმჯობესა ბეკის დეპრესიის ინდექსის (BDI) შედეგები, რაც 34%-ით გაიზარდა. ლიტერატურიდან ვიცით, რომ წინა კვლევებში დადებითი შედეგები 13%-დან 52%-მდე მერყეობდა. მიუხედავად იმისა, რომ საჭიროა დამატებითი კვლევები, ბოტულინის ნეიროტოქსინის თერაპია შესაძლოა ეფექტური და ინოვაციური მიდგომა იყოს დეპრესიასთან ბრძოლაში.

Introduction. In today's rapidly evolving field of medicine, the battle against certain diseases continues to persist, casting a shadow over the lives of many individuals. Among these afflictions, depression stands out as a formidable foe, often resistant to conventional treatment methods [1].

Depression is a common mental health disorder characterized by persistent feelings of sadness, hopelessness, and loss of interest in activities. It can have a significant impact on a person's daily life, relationships, and overall well-being. According to the World Health Organization, depression is the leading cause of disability worldwide, affecting over 280 million people globally and an estimated 5% of adults suffer from it [2].

Current treatment options for depression include psychotherapy, medication, and in severe cases, electroconvulsive therapy [3]. While these treatments can be effective for many individuals, there is a need for alternative therapies for those who do not respond to traditional approaches. It is estimated that up to one-third of individuals, about 30% of patients diagnosed with depression do not respond adequately to traditional antidepressant medications or psychotherapy [4]. This condition is often referred to as treatment-resistant depression (TRD). For these individuals, finding an effective treatment and alternative approaches can be challenging [5,6,7].

One emerging treatment option for depression is Botulinum Neurotoxin therapy. Botulinum Neurotoxin, commonly known as Botox, is a neurotoxic protein produced by the bacterium *Clostridium botulinum*. Originally used for cosmetic purposes to reduce wrinkles [8], researchers have been exploring its potential therapeutic benefits for various medical conditions, including depression [9].

Botulinum Neurotoxin Therapy for Depression. Botulinum Neurotoxin therapy works by blocking the release of acetylcholine [10], a neurotransmitter that plays a role in muscle contraction and communication between nerve cells [11]. In the context of depression, researchers believe that Botulinum Neurotoxin may disrupt the feedback loop between facial expressions and emotions, leading to a reduction in negative emotions associated with depression [12].

Several studies have shown promising results in using Botulinum Neurotoxin therapy for depression. A study published in the *Journal of Psychiatric Research* found that patients with major depressive disorder who received Botulinum Neurotoxin injections in the glabellar region (between the eyebrows) experienced significant improvements in their depressive symptoms compared to a control group [13]. Another study published in the *Journal of Clinical Psychiatry* reported similar findings, with participants showing reduced depression scores after receiving Botulinum Neurotoxin injections in the forehead region [14]. These researches have unveiled its potential as a therapeutic agent for conditions beyond aesthetic concerns.

Future Perspective. While the use of Botulinum Neurotoxin therapy for depression is still in its early stages [15], researchers are optimistic about its potential as a novel treatment option. One of the key advantages of Botulinum Neurotoxin therapy is its relatively low risk of adverse effects compared to traditional antidepressant medications. Additionally, Botulinum Neurotoxin injections are minimally invasive and do not require daily dosing, making it a convenient option for patients who may have difficulty adhering to medication regimens [16].

More research is needed to fully understand the therapeutic mechanisms and long-term effects of Botulinum Neurotoxin therapy for depression. Future studies should focus on identifying the optimal dosing regimen, patient selection criteria, and potential biomarkers to predict treatment response [17].

Mechanisms of Botulinum Neurotoxin Therapy for Depression:

1. *Explanation of how Botulinum Neurotoxin works:* Botulinum Neurotoxin, produced by the anaerobic, spore-forming, rod-shaped bacterium, *Clostridium botulinum* [18], commonly known as Botox, manifest in seven identified serotypes (A-G), each comprising a molecular weight of 150 kDa, divided into a light chain (LC; 50 kDa) and a heavy chain (HC; 100 kDa). Primarily, BoNTs act at the neuromuscular junction, inducing flaccid paralysis by hindering neurotransmitter release from peripheral cholinergic nerve terminals within the skeletal and autonomic nervous system. BoNTs represent bacterial exotoxins targeting intracellular substrates. Their structure allows the metalloprotease domain to enter the host cell cytosol, taking advantage of nerve terminal functions.

Local BoNT injection reduces muscle fiber activity by inhibiting acetylcholine release from nerve terminals. It achieves this through various transport mechanisms, including binding, internalization, membrane translocation, disulfide reduction, and SNARE protein cleavage. These processes involve endocytosis, intracellular trafficking, and possibly FGFR3 activation. BoNT/A can reach the central nervous system from the injection site, affecting central neuronal circuits. BoNT/A1 can also move from the periphery to the CNS, influencing CNS neurons and sensory nerves through retrograde and anterograde transport, which suggests an active transport mechanism rather than passive diffusion.

2. *The role of facial expressions in depression:* It is commonly believed that our emotions influence our facial expressions, yet the impact of our facial expressions on our emotions is often overlooked.

Nonetheless, ample evidence indicates that our facial expressions serve as a tangible method for encoding and conveying emotional messages. Facial expressions play a significant role in the experience and expression of emotions. The facial feedback hypothesis suggests that our facial expressions can influence our emotions, with certain expressions triggering corresponding emotional responses. For example, frowning or furrowing one's brow can signal sadness or distress, while smiling can convey happiness or joy [19]. In depression, individuals may exhibit more negative facial expressions, which can reinforce negative emotions and contribute to the persistence of depressive symptoms.

3. The theory behind Botulinum Neurotoxin therapy for depression: Various facial expressions such as frowning and sadness can also be easily recognized in depressed patients. These facial expressions, which involve muscles in the glabellar regions of the face, have been found to be overactive in depressed patients. This overactivity of facial muscles associated with negative emotions may contribute to the development and persistence of depressive symptoms.

Based on the facial feedback hypothesis, researchers have proposed that by temporarily paralyzing specific facial muscles with Botulinum Neurotoxin injections, it may disrupt the feedback loop between facial expressions and emotions. By preventing the ability to make certain negative facial expressions associated with depression (such as frowning), Botulinum Neurotoxin therapy could potentially reduce the intensity of negative emotions and improve mood in individuals with depression. This theory suggests that altering facial expressions through Botulinum Neurotoxin injections may lead to a positive impact on emotional well-being and depressive symptoms [20].

The amygdala plays a central role in regulating negative emotions such as sadness, anger, and fear, and is implicated in the pathogenesis of various psychiatric disorders. Treatments that target the amygdala have been found to induce rapid antidepressant effects. Studies using botulinum toxin injections to temporarily inhibit facial muscles associated with the amygdala have demonstrated a direct link between muscle activity and amygdala regulation [21].

The injection of botulinum toxin type A (BoNT/A) into the corrugator muscles of depressed individuals serves as a specific and significant test that builds upon decades of research into the underlying mechanisms of depression. Studies have revealed that dysfunction in the amygdala-ventromedial prefrontal cortex pathway is linked to major depressive disorder (MDD). When BoNT/A is injected into the glabellar region to temporarily paralyze the procerus and corrugator muscles, there is a noticeable modulation of amygdala activity, as evidenced by functional magnetic resonance imaging (fMRI). In response to viewing angry facial expressions, the typical increase in amygdala activity is reduced when muscle contractions are inhibited by BoNT/A. Furthermore, after the effects of BoNT/A wear off, amygdala activity returns to its original state, demonstrating the reversible nature of BoNT/A in regulating amygdala function.

Additionally, Botulinum toxin injections have been found to have anti-inflammatory effects, which may be relevant in the context of depression. Botulinum toxin injections have been shown to modulate neuroinflammation [22], which is believed to play a role in the development and progression of depression.

In suicidal depressed patients, BDNF (Brain-Derived Neurotrophic Factor) levels are found to be significantly lower [29], similar to serotonin levels. BoNT/A, in addition to its cosmetic effects, has been shown to increase BDNF levels. This could have a positive impact on individuals, as BDNF plays a crucial role in promoting neuronal health and growth. Our goal is to review previous researches and make this information available on a larger scale so that clinicians can access similar therapies for use in unconventional cases. The purpose of the study was not to directly cure depression, but to evaluate the

positive impact that manipulations carried out for aesthetic purposes would have on their general mood and condition.

| Nº | Gender | Age | Primary Data | Final Data | Difference | Results |
|----|--------|-----|--------------|------------|------------|---------|
| 1 | Female | 44 | 41 | 7 | 34 | SGI & R |
| 2 | Female | 33 | 38 | 9 | 29 | SGI & R |
| 3 | Female | 29 | 35 | 6 | 29 | SGI & R |
| 4 | Female | 42 | 39 | 11 | 28 | SGI & R |
| 5 | Female | 32 | 32 | 6 | 26 | SGI & R |
| 6 | Female | 43 | 20 | 0 | 20 | SGI & R |
| 7 | Female | 38 | 34 | 15 | 19 | CMI |
| 8 | Female | 28 | 34 | 19 | 15 | CMI |
| 9 | Male | 41 | 27 | 14 | 13 | CMI |
| 10 | Female | 42 | 22 | 10 | 12 | CMI |
| 11 | Female | 41 | 17 | 7 | 10 | CMI |
| 12 | Male | 37 | 11 | 4 | 7 | NSI |
| 13 | Female | 39 | 14 | 7 | 7 | NSI |
| 14 | Male | 29 | 17 | 15 | 2 | NSI |
| 15 | Female | 62 | 5 | 3 | 2 | NSI |

Methods: The study involved 15 participants and it lasted on average two months. The Beck Depression Inventory (BDI) Questionnaire, in total 21 question, was used for assessment. The inclusion criteria were lack of hypersensitivity to Botox, satisfaction with enrollment in the study, awareness of depression and no other treatment for depression in history. The scores of BDI were determined and compared at baseline and after 9 or 12 weeks in the participants. At the beginning 86.67% of patients (66.67% males, 91.67% females) had an increased score. Botulinum Neurotoxin was injected in the glabellar region, in the corrugator and procerus muscles.

Table 1

| | female | male | results | meaning |
|---------|--------|------|---|-------------------------|
| NSI | 2 | 2 | Numerically successful improvement | Activity but no changes |
| CMI | 4 | 1 | Clinically meaningful improvements | Modest improvements |
| SGI & R | 6 | | Significantly greater improvement and response rate | Significant progress |

Review of the previous researches. In 2006, Finzi and colleagues were the first to document that the use of BoNT/A in 10 individuals with depression resulted in a significant enhancement in self-reported depression scores as measured by the Beck Depression Inventory II (BDI-II) [9]. After receiving BoNT/A injections, nine patients showed reduced depression two months later, and one patient experienced a positive change in mood. This led to further research on the therapeutic benefits of BoNT/A for depression, resulting in several randomized controlled trials. These trials mainly focused on injecting BoNT/A into frown muscles and the glabellar area, with some also exploring other injection sites [24]. The

concentration of BoNT/A injected varied, with 29 units administered in females and 39 to 40 units in males across five reports. Clinical assessments of depression were conducted using the Montgomery Asberg Depression Rating Scale (MADRS), BDI-II, and Hamilton Depression Scale (HAMD), revealing a remission rate exceeding 50% post-treatment with BoNTs. Notably, females exhibited a higher remission rate compared to males. However, the duration of this study was limited to only 6 weeks [25].

In a separate study by Finzi in 2018, it was demonstrated that BoNTs injections were also effective in treating bipolar depression in men [26]. A randomized, placebo-controlled trial was conducted to explore the potential benefits of injecting BoNT/A into the glabellar area as an adjunct therapy for depression. This trial spanned 16 weeks and enrolled thirty participants who were randomly assigned to receive either BoNT/A (n = 15) or saline (n = 15) injections. The response rates for the BoNT/A and placebo groups were 60.0% and 13.3%, respectively. The findings suggested that a single injection of BoNT/A in the glabellar region could lead to rapid and sustained remission in depressed patients who had not responded to previous medications.

Lewis and colleagues assessed the impact of BoNT/A on mood by comparing patients who underwent BoNT/A therapy in the glabellar region with those who received other cosmetic treatments [27]. The study included 25 female participants, with the BoNT/A treatment group exhibiting lower scores on the Irritability-Depression-Anxiety Scale (IDAS) compared to the control group. The geometric mean remission duration was found to be 195 days, which was the longest reported duration.

In a study by Brin et al., they examined the effects of BoNT/A on depression in females using two different doses: 30U and 50U. After 6 weeks, the group receiving 50U did not show significant differences compared to the placebo group. However, the group receiving 30U displayed consistent efficacy over 12 weeks or more, as measured by multiple depression symptom scales. The differences between the BoNT/A (30U) and placebo groups on the MADRS scale were clinically relevant, meeting the threshold for significance in Major Depressive Disorder (MDD).

Another study by Magid and colleagues investigated the impact of BoNT/A over a 24-week period. They found that the group receiving BoNT/A as the first treatment had a response rate of 55%, while the group receiving it as the second treatment had a response rate of 24%. In contrast, the placebo group had a response rate of 0%. The study also showed a significant reduction in BDI scores after the initial injection of BoNT/A. Patients with persistent glabellar frown lines were given an additional dose of up to 20 units. [28]. Overall, these clinical trials support the potential effectiveness of BoNT/A in treating depression [23].

Results. Advantages and Disadvantages of Botulinum Neurotoxin Therapy:

Advantages:

- **Rapid onset of action:** Botulinum Neurotoxin injections have been shown to produce improvements in depressive symptoms within days to weeks, compared to the delayed onset of action seen with some antidepressant medications [23].
- **Minimal systemic side effects:** Botulinum Neurotoxin therapy is generally well-tolerated and does not typically cause the systemic side effects associated with antidepressant medications.
- **Targeted treatment:** Botulinum Neurotoxin injections can be administered directly to specific facial muscles involved in expressing negative emotions, offering a targeted approach to addressing depressive symptoms.

Disadvantages:

- **Temporary effects:** The effects of Botulinum Neurotoxin therapy for depression are temporary and typically last for several months. Repeat injections may be necessary to maintain the benefits.

- Cost: Botulinum Neurotoxin injections can be expensive, especially if not covered by insurance, making them less accessible to some individuals.
- Limited long-term data: Long-term studies on the safety and efficacy of Botulinum Neurotoxin therapy for depression are still limited, raising questions about its long-term effects and sustainability as a treatment option.

Patient BDI scores after BoNT/A treatment

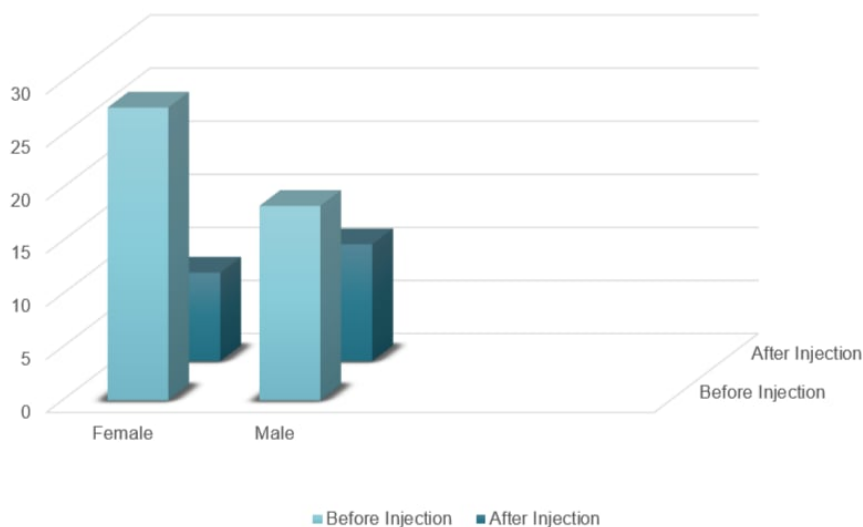


Table 2: Patient BDI scores after BoNT/A treatment.

The study results (Table 2, 3) were not only promising but also pleasant, offering valuable insights into the potential positive impact of Botox in the treatment of depression. The administration of BoNT/A injections resulted in a noteworthy enhancement in self-rated depression scores, as assessed through the widely recognized Beck Depression Inventory (BDI). The response rates observed with BoNT/A therapy were particularly encouraging, reaching an impressive 34%. This figure falls within the range of positive response rates reported in previous studies, which have varied from 13% to 52%, further underscoring the potential efficacy of BoNT/A in managing depression. These findings provide compelling evidence of the therapeutic benefits that Botox may offer to individuals struggling with depression, opening up new avenues for treatment and enhancing our understanding of its potential role in mental health care.

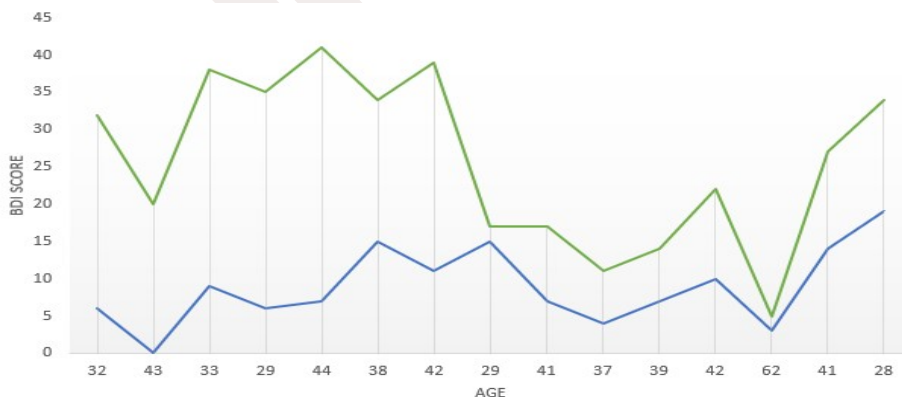


Table 3: Patient BDI scores of the BoNT/A treatment

Before injections
After injections

Discussion. Potential future applications of Botulinum Neurotoxin therapy for depression include combining it with psychotherapy or other drugs, optimizing dosing and injection sites for better outcomes, and studying its long-term effects on depressive symptoms and quality of life. Advancements in

technology and research could lead to more targeted formulations of Botulinum Neurotoxin for depression treatment. Improved neuroimaging techniques could also help understand how the toxin affects neural pathways involved in depression. Ethical considerations and potential risks of Botulinum Neurotoxin therapy for depression include obtaining informed consent, monitoring for side effects, and addressing concerns about cosmetic versus therapeutic use. Researchers and clinicians must carefully weigh the benefits and risks and prioritize the well-being of patients. However, measuring depressive symptoms and mood improvement is subjective, despite the use of standardized scales and assessments.

Conclusion. Botulinum Neurotoxin therapy for depression shows potential benefits by inhibiting negative facial expressions to impact mood. However, criticisms include limited understanding of the mechanism, temporary effects requiring repeat injections, and lack of long-term safety and efficacy data. Ethical concerns involve altering natural facial expressions, off-label use, and commercialization. Real case studies and clinical evidence are needed to explore effectiveness and safety further. Healthcare providers should consider individual needs and preferences when discussing treatment options. Continued research and ethical considerations are crucial for shaping the role of Botulinum Neurotoxin therapy in managing depression.

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NATO KAKABADZE^{1,2}, *NERIMAN TSINTSADZE*^{1,2}, *MIKHEIL ARTMELADZE*^{1,2},
*ALBINA KADJAJA*³, *MURAT TSINTSADZE*³, *NINO TSINTSADZE*¹

IMPACT OF THE BOTULINUM NEUROTOXIN INJECTIONS ON PATIENTS WITH DEPRESSION: THERAPEUTIC MECHANISMS AND POSSIBLE FUTURE PERSPECTIVE

¹Avicenna - Batumi Medical University, Batumi, Georgia; ²“SoloMed” Clinic, Batumi, Georgia; ³Total Charm Vake, Tbilisi, Georgia

SUMMARY

Background: Despite the fact that today's medicine is constantly developing in all directions, there are still some diseases that burden humanity and interfere with daily life, like Depression. Existing treatment tactics are often ineffective, and Botox injections in such cases are an experimental method.

Objectives: Our goal is to review previous researches and make this information available on a larger scale so that clinicians can access similar therapies for use in unconventional cases. The purpose of the study was not to directly cure depression, but to evaluate the positive impact that manipulations carried out for aesthetic purposes would have on their general mood and condition. Our attention was especially drawn to the fact that research on this topic has not been conducted in our country yet.

Methods: The study involved 15 participants and it lasted on average two months. The Beck Depression Inventory (BDI) Questionnaire, in total 21 question, was used for assessment, just like our predecessors.

Results: The results, to our delight, gave us very interesting feedback, based on which we can assume the positive contribution of Botox in the management of patients with depression. BoNT/A injections led to significant improvement of self-rated depression score by using Beck Depression Inventory (BDI). The response rates of BoNT/A were 34%. From the literature, we know that positive results in previous studies ranged from 13% to 52%.

Conclusion: Botulinum Neurotoxin therapy shows promise as a novel approach to treating depression. While further research is needed to establish its effectiveness, Botox may offer a unique and potentially valuable option for individuals struggling with depression.

Keywords: depression, botulinum neurotoxin, therapy, facial feedback, Beck Depression Inventory (BDI)

