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Botox or the new face of the fight against depression - literature review

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ABSTRACT

Introduction: Depression is a common psychiatric disorder leading to high burden especially for some other psychiatric comorbidity. Annually over 43 billion dollars are expended for patients with depression among them 28% are directly for depression and other costs are related to mortality and morbidity due to depression.

The aim of the study: Paying attention to new options for treating depression – a disease that affects more and more people.

Material and method: The research was done by the usage of the PubMed and Google Scholar articles about the topic of: botulinum toxin; depression; treatment.

Description of the state of knowledge: Injecting Botox into the muscles responsible for expression of anguish or sadness may potentially decrease the patients experience of feelings. Botox reversibly blocks acetylcholine release from neuronal axons into the synapse, inhibiting neuromuscular transmission. If the facial feedback hypothesis is correct, by injecting Botox into the corrugator and procerus muscles, it will reversibly inhibit frown facial expressions and have the capability of propagating or enhancing sad and depressed feelings.

Summary: The results from all randomized control trials proved that botulinum toxin A injection in the glabellar region was associated with significant improvement mood and may be a safe and effective treatment to reduce symptoms of depression.

Key words: botulinum toxin; depression; treatment;

Introduction

Depression is a common condition affecting over 300 million people around the world. There are many known treatments for depression, however in long-lasting, moderate-to-severe conditions, depression can, in some cases, lead to suicide. The facial feedback hypothesis states that facial musculature not only expresses mood states, but also regulates them. By contracting a specific muscle, humans can create an emotion and, conversely, by relaxing those muscles, they can minimise an emotion. Botulinum toxin type A is a neurotoxin which acts as a blocking agent, leading to muscles being temporarily weakened or paralysed. Numerous studies have shown the link between a reduction in depressive symptoms and the treatment of the glabella with botulinum toxin type A injections. The manufacturer of Botox (Allergan) has continued with this research and, in 2017, it announced data from a phase 2 study supporting the advancement of botulinum toxin type A for the treatment of major depressive disorder. The company will now be moving the drug forward to a phase 3 programme for a potential new treatment for patients [1].

Depression

Major Depressive Disorder (MDD) is an illness that affects 16% of the US population, more than 350 million people worldwide, and is a leading cause of disability internationally [2]. In the most recent surveys, MDD has the highest lifetime prevalence of any psychiatric disorder and patients are at an increased risk for additional comorbid disorders such as alcohol abuse, panic disorder, obsessive compulsive disorder and social anxiety [3].

The exact etiology of MDD is not clearly defined; however, it is thought to be due to either long term effects of chronic stress on the brain from increased cortisol and CRH or from a decrease in monoamines (dopamine, serotonin, norepinephrine) causing the brain to up-regulate monoamine receptors leading to depression [4]. The diagnosis of MDD is obtained through a good clinical history [3]. The diagnosis is based on the patient having at least 5 symptoms (one must be depressed mood or anhedonia) for 2 weeks [4]. The symptoms include: sleep disturbance, feeling of guilt, decreased energy, decreased concentration, appetite change, psychomotor agitation, and suicidal ideations.

The most effective intervention for achieving remission and preventing relapse is medication, but combined treatment, incorporating psychotherapy to help the patient cope with decreased self-esteem and demoralization, improves outcomes [4]. The available antidepressants do not differ in overall efficacy however, they do differ in their pharmacology, drug-drug interactions, short- and long-term side effects, likelihood of discontinuation symptoms and ease of dose adjustment [3].

Botox – "miracle poison"

Botulinum toxin is often referred to as the "miracle poison" because it is a highly lethal neurotoxin that has a variety of cosmetic and clinical applications [5]. Produced by the bacterium Clostridium botulinum, botulinum toxin prevents the release of acetylcholine into the neuromuscular junction, producing a temporary (3–6 month) weakness or paralysis in the injected muscle [6]. Botulinum toxin is commonly injected in the glabellar facial region—a treatment henceforth referred to as GBTX—to temporarily correct frown lines by inhibiting muscular activity in the corrugator supercilii and procerus facial muscles [7]. However, although the purpose of this widely sought treatment is typically cosmetic (American Society for Aesthetic Plastic Surgery, 2016; International Society of Aesthetic Plastic Surgery, 2016), researchers have recently proposed that it may also have a fortuitous side effect: reducing clinical depression.

By using a bacterial neurotoxin to paralyze facial muscles, Botox treatments get rid of wrinkle lines. They can also make it hard to frown. That has led some clinicians to the unusual idea that, by eliminating the negative emotional feedback that frowns feed the brain, Botox can also be used to treat depression.

Researchers have suggested that the botulinum toxin "miracle poison" can reduce clinical depression. More specifically, they speculate that (a) inhibiting the contraction of frowning muscle via GBTX will attenuate patients' negative emotional experiences, (b) reductions in negative emotional experiences will subsequently lead to improvements in clinical depression [8].

Process physiology

Botulinum toxin type A (BoNTA) is the exotoxin of Clostridium botulinum, a spore-forming, Gram-positive anaerobic bacterium [9]. BoNTA is a neurotoxin which works within cholinergic synapses present at neuromuscular endplates, preventing the transmission of neurotransmitters, such as acetylcholine, from nerves to muscles [10]. Normally, when a muscle is required to contract, a nerve sends a signal to the muscle and this signal reaches the neuromuscular junction. At this point, acetylcholine is released from the nerve side of the junction and binds to the muscle side, causing contraction of the muscle. When BoNTA is injected into the muscle, acetylcholine is unable to bind to its receptor on the muscle. This interference with nerve impulses leads to the muscles being temporarily weakened (paralysis) [1, 10].

While the notion that treatment of frown lines could improve the mood of patients with depression may seem far-fetched, the rationale is based on the facial feedback hypothesis. The facial feedback hypothesis dates back to research carried out by Charles Darwin in 1872 [11]. It suggests that when people make a facial expression, there is feedback from the muscles in the face that can modulate the subjective experience of emotion [12]. Activation of the corrugator and procerus muscles in the glabella region are associated with negative emotions prevalent in depression, such as anger, fear and sadness [1, 13].

One potential theory for the reduction of depressive symptoms with onabotA treatment is the ‘facial feedback hypothesis', which states that expressive behavior can alter emotional states, likely through afferent sensory modulation [14,15]. The simple act of frowning may lead to a reduction in serotonin, for instance, whereas smiling can up-regulate the system. Corrugator muscles, which are activated during negative emotions (e.g. fear, anger, and sadness) [13], are relatively over-reactive in patients with depressive disorders [16]. Imaging studies have shown that when subjects, without a history of psychiatric illness, mimicked angry expressions, they demonstrated decreased left amygdala activity after treatment with botulinum toxin in the glabellar region in addition to reduced functional coupling between left amygdala and dorsal brainstem [17]. The decreased activity may be attributed to the reduction in motor nerve activity associated with dynamic facial expressions and/or proprioceptive sensory input following local treatment. Furthermore, facial somatic sensory afferents synapse in the descending trigeminal nucleus with monosynaptic connections to amygdala [18], hypothalamus [19], nucleus accumbens [20], and thalamus [21], suggesting a pathway for facial afferents to directly influence limbic networks.

Test results

The definition of beauty is subjective, but undoubtedly todays culture places great emphasis on beautiful appearance. Beauty is self-confidence, well-being. Therefore, it can be expected that improving the appearance, even with minor intervention, can prevent depression and even cure some of its degrees.

General assumption is that facial expressions reflect rather than direct people’s emotions; however, much evidence suggests that facial expressions are not secondary to, but rather a central driving force of people’s emotions – in 2013, Finzi carried out a clinical trial in which BoNTA was placed into the frown muscles of 10 patients [22]. Two months later, the majority of the patients in the clinical trial were no longer clinically depressed according to

Diagnostic and Statistical Manual of Mental Disorders (fourth edition) (DSM-IV) criteria or their Beck Depression Inventory-II (BDI-II) test scores [22]. It was also noted that some of the patients did not have any visible frown lines before the treatment, which suggested that the results were not simply due to looking better, as there was no cosmetic improvement.

Research carried out by Strack et al [23] examined whether facial feedback could influence perception of emotion. Participants were asked to watch cartoons while holding a pen with either their teeth only or between their lips. The rationale here was that while holding the pen with the teeth only, participants would be mainly contracting the zygomaticus major or the risorius muscles (the muscles used in the smile response), whereas when holding the pen between the lips, particpants were unable to contract these muscles. Participants perceived cartoons to be funnier while holding pens in their teeth rather than between their lips, which is consistent with the idea that activation of 'smile muscles' would feed back to enhance positive emotions [1]. One study showed that mimicking facial expressions of anger or fear, even with no emotional valence attached to the expression, can lead to significant changes in heart rate and temperature [2].

In 2006, Finzi et al. injected BTA into the frown muscles of 10 depressed females. Nine of the 10 patients were no longer depressed at their 2 month follow-up. In 2010, Wollmer et al. injected 15 patients with placebo and 15 patients with BTA in a randomized, double-blind, placebo controlled trial. There was a significant improvement in depression in the BTA versus placebo group (47.1% vs. 9.2% reduction in Hamilton Depression rating scores, respectively) (Wollmer 2012). In 2012, Finzi conducted a randomized, double-blind, placebo controlled trial in which 33 patients received BTA and 41 received placebo. Again, the BTA group showed a significant improvement in depression (47% vs. 20.6% reduction in Montgomery Asberg depression rating score) (Finzi 2012) [2].

The study by Khademi et al was conducted on 121 people who were examined by the Beck Depression Inventory II (BDI) questionnaire before and after botox injection in the face area, respectively. The mean depression score dropped from 18.9 ± 4.8 to 10.6 ± 2.9 during the follow-up time. The main determinants of improving depression score included young ages, higher educational level, and previous experiences of botulinum toxin use [24].

In the Wollmer et al. study, there were 30 participants divided equally between the Botox group and the placebo group. After 6 weeks of treatment, the Botox recipients' symptoms were reduced by 47.1% and the placebo by 9.2%. The study also supported previous evidence with statistical findings ($p=0.002$) that MDD symptoms improve with the use of Botox [25].

In the study Zamanian et al 28 patients with major depression were randomized to botox and a placebo. The scores of Beck Depression Inventory were determined and compared at baseline and after two and six weeks in the groups and between the groups. In addition, the drug adverse effects were compared between groups. The mean depression score dropped from 30.86 to 19.00 during the follow-up time [26].

Magid et al recruited 30 patients with moderate to severe frown lines due to over-activity in the glabellar region, and injected BTA into this area. At baseline visit (week 0), patients were randomized to receive either onabotulinumtoxin A at a concentration of 25 units/1 ml dissolved in 0.9% NaCl saline solution, or placebo, 0.9% NaCl saline solution. Identical volumes of placebo or active substance were placed in 30G syringes and were injected into the glabellar region at five specific points. Women received 29 units (U), 7 U in the procerus,

6 U bilaterally to the corrugator muscles. At each visit, patients were assessed with the following objective measurement scales: the Hamilton Depression Rating Scale 21 (HAM-D 21) (physician administered), the Beck Depression Inventory (BDI) (self-rating), and the Patient Health Care Questionnaire 9 (PHQ-9) (self-rating). Active and placebo groups did not differ in age, education, number of psychotropic medications or duration of depression [2].

This study shows a statistically significant reduction in depressive symptoms in those who received botulinum toxin A versus placebo injections in the frown muscles. This is another study to date that has shown efficacy in the treatment of depression with botulinum toxin A, and the first to show continued improvement over a 24 week period of time, which is longer than any prior study has shown (i.e. Wollmer 2010 showed sustained improvement over 16 weeks, the duration of his study). This is particularly thought-provoking given that previous data suggest that the cosmetic effects of BTA last approximately 12-16 weeks. This indicates that the treatment not only suppresses the symptoms of depression as long as the paralytic effect is present, but has a persistent antidepressant effect that prevents immediate relapse once the paralysis wears off [2].

Conclusion

BTA is used in the cosmetic treatment of frown lines by inhibiting the activity of the corrugator and procerus muscles [10]. The impact of injecting the glabella region and the change of facial expression from angry or sad to happy influences emotional experience [27]. Studies have shown recipients to not only report an increase in emotional wellbeing beyond cosmetic benefit [28], but also a decrease in levels of fear and sadness [1, 29].

The facial feedback hypothesis suggests that facial expression can affect emotional perception. As we often talk about depression being a vicious cycle of biological changes affecting psychosocial functioning and vice-versa, BTA may be breaking this cycle by inhibiting a negative emotional circuitry and improving social interaction, which may explain why improvement in mood lasts beyond the cosmetic effects of the intervention. The treatment of depression using BTA is safe, effective, and may decrease both direct costs (e.g. medications, physician visits) and non-direct costs (loss of work productivity) of this disease. Preliminary cost effectiveness analysis has shown that this may be a less expensive intervention than psychotherapy or medications in specific patient populations (Beer 2010) [2].

In April 2017, Allergan revealed data from a phase 2 study supporting the advancement of Botox for the treatment of major depressive disorder (Allergan, 2017). The study was a proof of concept, phase 2, multicentre, randomised, double-blind, placebo-controlled, twodose cohort parallel group, single-treatment study in 258 females with moderate-to-severe major depressive disorder. In the three groups (30 U, 50 U and placebo), the 30 U dose lowered participants' Montgomery-Asberg Depression Rating Scale (MADRS) score by 3.6 points at week 6 compared with placebo [1].

In summary, trials adds to the growing body of evidence that botulinum toxin A in the glabellar region can treat depression. Furthermore, the effects on mood last beyond the cosmetic effects of BTA, suggesting that this intervention may break a cycle [2].

Given that a third of patients do not respond to antidepressants, this alternative treatment may be a viable option for millions of people suffering from this illness [2].

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