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Is Botox A Safe And Effective Treatment To Reduce Symptoms Of Depression?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not Botox is a safe and effective treatment to reduce symptoms of depression? Study Design: The review is based on three Randomized Control Trials that were double-blind and placebo controlled clinical trials. Data Source: All articles were researched and found using PubMed and Medline. The articles were selected based on the relevance to my clinical question and if the articles included patient oriented outcomes (POEMS).

Outcomes Measured: The outcomes were measured by the improvement of depressive symptoms (sleep disturbances, suicide ideations, change in appetite/weight/concentration/energy/guilt/interests) and improvement in scores from the Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (17 and 21), Beck Depression Inventory (BDI) and Patient Health Care Questionnaire-9.

Results: In the study by Finzi et al. (2013), they found statistical evidence ($p < 0.001$) that Botox improved symptoms of Major Depressive Symptoms. The evidence revealed that 52% of patients at 6 weeks showed signs of improvement compared to the placebo group whom showed a 15% improvement of symptoms. A study by Magid et al. (2014) also found statistical evidence ($p<0.001$) that treatment with Botox did improve symptoms of Major Depressive Disorder (MDD). The study showed that 55% of the patients who received Botox responded to treatment and had decreased symptoms with 0% of the placebo group showing any reduction in symptoms. A study by Wollmer et al. (2012) also supported the previous evidence with statistical findings ($p=0.002$) that MDD symptoms improved with the use of Botox. Patients had reduced symptoms on average of 47% with the use of Botox compared to the placebo group whom had a decrease in 9.2% of their symptoms.

Conclusion: The results from all three Randomized Control Trials proved that Botox is a safe and effective treatment to reduce symptoms of depression.

Key Words: Botulinum Toxins, Depression

INTRODUCTION

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.[8]

Although there was no exact estimate available for annual health care visits, we know that depression affects more than 15 million American adults, or about 6.7 percent of the U.S. population age 18 and older in a given year.[7] The economic burden of depression was estimated at $83.1 billion in 2000 in the United States.[5] For employed and treated patients, incremental direct costs of health care services were $5,707 per MDD patient in 2005, increasing by 5% in 2010 to $5,988.[5]

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.[6] The diagnosis of MDD is obtained through a good clinical history.[8] The diagnosis is based on the patient having at least 5 symptoms (one must be depressed mood or anhedonia) for 2 weeks.[6] The symptoms include: sleep disturbance, feeling of guilt, decreased energy, decreased concentration, appetite change, psychomotor agitation, and suicidal ideations.[6]

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.[6] The classes of antidepressant

medications are serotonin selective reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), norepinephrine dopamine reuptake inhibitor (NDRI), tricyclic antidepressant (TCA), and monoamine oxidase inhibitor (MAOI). The available antidepressants do not differ in overall efficacy, speed of response, or long-term effectiveness, 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.[8] A rational approach to selecting which antidepressant to use involves matching the patient's preference and medical history with the metabolic and side effect profile of the drug.[6]

Troubling side effects from the use of antidepressants, such as decreased libido, anorgasmia, insomnia and nausea, are a major reason why patients discontinue treatment and subsequently relapse.[1] A relevant proportion of patients do not sufficiently improve with medication management and psychotherapy and are often left with fewer therapeutic options.[2] The use of Ontabotulinumtoxin A (Botox) may be used as an adjunct to anti-depressant medications or psychotherapy for the treatment of depressive symptoms.

The theories behind why Botox may be effective for treatment of MDD and its mechanism of action is through the facial feedback hypothesis.[1] The hypothesis suggests that facial expression influences emotional perception; producing an expression that is characteristic of a particular emotion can lead to experiencing an emotion (eg, smiling can lead to happiness, scowling can lead to anger).[2] 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] Injecting Botox into the muscles responsible for expression of anguish or sadness may potentially decrease the patients experience of feelings.[1,2] Botox reversibly blocks acetylcholine release from neuronal axons into the synapse, inhibiting

neuromuscular transmission.[2] 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.[1]

OBJECTIVE

The objective of this selective EBM review is to determine whether or not Botox is a safe and effective treatment to reduce symptoms of depression.

METHOD

The studies that are evaluated in this systemic review are three randomized control trials that were double-blind with placebo controlled trials. The articles were researched through PubMed and Medline and all three articles were published in English between 2012 and 2014. The keywords that were searched in PubMed and Medline were "Botulinum Toxins" and "Depression". Articles were selected based on the relevance to my clinical question and if the articles included patient oriented outcomes (POEMS).

The criteria used for the selection of each study was based on the population study, intervention, comparisons group and the outcomes of each study. The population being studied in the three studies included men and women between the age of 18 and 65 with an ongoing diagnosis of MDD. Wollmer et al.[3] varied in that it only used patients between the ages of 25 and 65.

The intervention being used in all three studies was Ontabotulinumtoxin A, 29U for women and 39U for men. For women, 7U was injected into the procerus muscle and 6U was injected bilaterally to the medial part of the corrugator muscles and 5U bilaterally to the middle part of the corrugator muscle. For men, 9U was injected into the procerus muscle and 8U was injected bilaterally to the medial part of the corrugator muscles and 7U bilaterally to the middle part of

the corrugator muscle. The Botox was compared to the use of a placebo, 0.9%NaCl solution, which used the same number of units injected into the same locations as the Botox.

The inclusion criteria for all three studies included randomized control trials that were double-blind, all included relevant POEMS, all patients were over 18 years old, patients had an ongoing diagnosis of MDD, and all studies evaluated the efficacy of Botox on MDD. The exclusion criteria included patients that were under the age of 18, had an active substance abuse problem, had an unstable medical condition or had previous Botox treatments. The statistical analyses were reported by p-values, NNT, RBI and ABI. Table 1 represents the demographics and characteristics of each study.

OUTCOMES MEASURED

All three studies were measuring outcomes by improvement of major depressive symptoms and improvement of scores on self-rating questionnaires. Finzi et al. measured their outcomes based on the Montgomery and Asberg Depression Rating Scale (MADRS) and Beck Depression Inventory (BDI) which is filled out by the patient and the Clinical Global Impression (CGI) which is filled out by a clinician.[1] Magid et al. measured their outcomes primarily with patient questionnaires such as the Patient Health Care Questionnaire-9, BDI and 21-item Hamilton Depression Rating Scale.[2] Wollmer et al. measured outcomes using the 17-item Hamilton Depression Rating Scale, BDI, CGI scale and four-point clinical severity score for Glabellar Frown Lines.[3]

Table 1: Demographics and characteristics of included studies

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Finzi (2013)[1]	Double Blind RCT	85	18-65	Outpatient men and women aged 18-65 with a DSM-IV diagnosis of MDD. Patients must have MADRS score >26 and a Clinical Global impression Severity >4.	Patients with another Axis I disorder, substance abuse history, illicit drug use, attempted suicide in past 6 months, unstable medical condition, treated with OBA in past 12 months, change in medication regimen	0	Single injection of OntabotulinumtoxinA vs. placebo group receiving 0.9% NaCl (29U for women and 39U for men)
Magid (2014)[2]	Double Blind RCT	30	18-65	Men and women ages 18-65 with a history of MDD for at least 6 months as defined by DSM-IV criteria. Patients must have scored a 14 or greater on the 21-Item Hamilton Depression Rating Scale	Active substance abuse, bipolar disorder, pregnancy, unstable medical condition, previous Botox treatment, treatment with > 3 psychotropic medications, another axis H comorbidity	0	Single injection of OntabotulinumtoxinA vs. placebo group receiving 0.9% NaCl (29U for women and 39U for men)
Wollmer (2012)[3]	Double Blind RCT	30	25-65	Men and women age 25-65 with a diagnoses of on-going MDD and taking 1-2 antidepressants for at least 4 weeks and have a moderate to severe vertical glabellar line.	Psychotic symptoms, suicide tendency, untreated depressed, another DSM-IV axis I diagnosis, personality disorder, severe PMS/PMDD, regular migraines, contraindications of Botox, previous treatment with Botox	0	Single injection of OntabotulinumtoxinA vs. placebo group receiving 0.9% NaCl (29U for women and 39U for men)

RESULTS

All three randomized control double-blind trials in this systemic review used the methods previously described to determine the efficacy of using Botox to treat MDD in comparison to a placebo of 0.9% NaCl over a six-week period.

In the study by Finzi et al.[1], 74 subjects were randomly selected in the double-blind study, 33 in the Onabotulinumtoxin A group (OBA) and 41 in the placebo group with very minor demographic differences between the OBA group and placebo group. The participants were required to complete initial MADRS questionnaires. The participants were followed up with the same questionnaires at week 3 and week 6 to determine the efficacy of Botox. At week 6, 52% of the participants in the OBA group had improved depressive symptoms compared to the 15% in the placebo group. The two groups were compared statistically by calculating a p-value of <0.001. Since the p-value is < 0.5 the treatment is statistically significant. Table 3 outlines the mean MADRS scores between the OBA group and the placebo group. The table outlines a significant decrease in scores in the OBA group at week 0 (31.6) and week 6 (16.9) in comparison to a slighter decrease in the placebo group at week 0 (31.2) and week 6 (24.6).

Table 2: Mean MADRS scores over time

	Week 0	Week 3	Week 6
OBA	31.6	18.9	16.9
Placebo	31.2	24.9	24.6

In the Magid et al.[2] study, there were 30 participants enrolled with 11 patients receiving Onabotulinumtoxin A (BTA group) and 19 in the placebo group. Participants were monitored at week 0, week 6, week 12 and week 24. This study included a crossover at week 12, however, analysis was given for the initial 6 weeks then again after the crossover at week 24. In an attempt to compare equivalent data, only the data from week 6 of each trial was used in this systemic

review. At week 6, the response rate for BTA group was 55% and 0% for the placebo group. The study found statistical evidence ($p < 0.001$) that treatment with Botox did improve symptoms of MDD.

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.

Dichotomous data was used in all three studies. The Relative Benefit Increase (RBI), Absolute Benefit Increase (ABI) and Numbers Needed To Treat (NNT) were calculated for all three studies to determine the efficacy of Botox after six weeks of treatment. The data can be found in Table 3. The NNT for all three studies shows that for every 2-3 patients treated with Botox, one more will have benefit of treatment from Botox and relief of symptoms at six weeks compared to the control group.

Table 3: Efficacy of Onabotulinumtoxin A in MDD symptoms at six weeks

	CER	EER	RBI	ABI	NNT
Finzi et al.	15%	52%	71.15%	37%	2.7
Magid et al.	55%	0%	100%	55%	1.8
Wollmer et. al	9.2%	47.1%	80.9%	37.9%	2.6

Safety and tolerability was evaluated in the Finzi et al. and Wollmer et al. study. Table 4 shows the analysis of safety and tolerability of Botox and the placebo (NaCl 0.9%) in both studies by calculating the Numbers Needed To Harm (NNH). In the Finzi et. al study the NNH was -7.5 meaning that for every 7.5 patients exposed to the treatment, 1 fewer will develop an adverse reaction compared to the control group. Only 3 adverse reactions occurred during the study and 2 of the 3 occurred in the placebo group. In the placebo group one patient experienced

vivid dreams and headaches while the second participant experienced headaches. In the experimental group only one patient complained of headaches. In comparison, the Wollmer et al. study had a NNH of -50 meaning that for every 50 patients treated with Botox, 1 fewer will develop an adverse reaction compared to the control group. The main adverse effects in this study included short episodes of headaches during the first few weeks of trial and occurred in both the experimental and placebo group. There were no adverse reactions noted or evaluated in the Magid et al. study.

Table 4: Safety and Tolerability of Botox vs Nacl 0.9% injection

	CER	EER	RRI	ARI	NNH
Finzi et al.	40%	26.7%	-33%	-13.3%	- 7.5
Wollmer et. al	5%	3%	-0.4	-2	- 50

DISCUSSION

Botox is currently FDA approved for many conditions in adults such as chronic migraines, upper limb spasticity, cervical dystonia, axillary hyperhidrosis, blepharospasm, and strabismus.[9] The contraindications to use of Botox are any hypersensitivity reactions or infection at the site of injection. There are many adverse reactions with the use of Botox for other conditions that range from non-life threatening such as headaches to life threatening such as death. For example, Botox used for cervical dystonia most commonly causes an adverse reaction of dysphagia but can also weaken accessory muscles that are necessary for adequate ventilation.[9] If these muscles were to become weakened and the use of Botox was continued patients could develop swallowing or breathing difficulties ultimately leading to death.[9] The three studies evaluated in this systemic review resulted in only non-life threatening adverse reactions, most notably headaches.

There were many limitations noted about all three studies. All three studies included a small sample size of either 30 or 85 participants which may not provide enough sufficient evidence to represent the true effectiveness of Botox in the MDD population. All three studies were also female dominant with 93% of the Finzi et al. participants, 90% of the Magid et al. participants and 78% of the Wollmer participants being female. Having a majority of the participants being female does not provide any statistical analysis of effectiveness based on gender. In addition, all three studies used Botox as an adjunct therapy to antidepressants or psychotherapy and not as monotherapy.

CONCLUSION

Based on the systemic review, Botox is a safe and effective treatment to reduce the symptoms of depression; however, it is not proven if Botox is an effective treatment as monotherapy to reduce the symptoms of depression. All three studies showed significant improvement of MDD symptoms with the use of Botox in the experimental group versus the controlled group in a six-week period.

Future studies need to evaluate the use of Botox as monotherapy. This would allow the treatment to be cost effective and patients would be more compliant as they would not have to remember to take a medication every day. Future studies should also consider evaluating the subjects for a longer duration to be able to provide adequate information on the length of time each injection could potentially last. Additionally, more research should be done to evaluate the potential long-term side effects from the use of Botox as continual therapy.

In conclusion, the systemic review proved that Botox is a safe and effective treatment to reduce the symptoms of depression; however, continued research should be done to evaluate the use of Botox as monotherapy and as long-term treatment.

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