OnabotulinumtoxinA Injection for Glabellar Frown Lines as an Adjunctive Treatment for Depression

By

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Declaration

I, the undersigned, hereby declare that the work in this thesis titled **OnabotulinumtoxinA Injection for Glabellar Frown Lines as an Adjunctive Treatment for Depression** is my own work and has not previously been submitted for any degree or examination at any university. All the sources that I have used or quoted have been indicated and acknowledged by means of complete references.

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I.Witbooi **Date**

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Abstract

Depression is one of the most prevalent mental disorders worldwide. Sadness, fear and anger which are considered as negative emotions and are common in depression are coupled with the stimulation of the *Corrugator supercilli* and procerus muscles in the glabellar area of the face. It has been suggested that OnabotulinumtoxinA (Botox®) administered into brow muscles to treat glabellar frown lines may improve emotional states. This study aimed to investigate the effectiveness of Botox® injection for glabellar frown lines as an adjunctive treatment for Major Depressive Disorder. The objective was also to determine whether Botox® injections administered in glabellar frown lines improve quality of life and self-esteem.

Twenty seven (27) participants diagnosed with major depressive disorder were randomly assigned to either the treatment group (Botox®, n = 12), placebo group (saline, n = 8) and the control group (n = 7). Participants in the treatment group or placebo group were injected with Botox® or saline solution in their procerus and *Corrugator supercilli* muscles at baseline and at week 12. The control group received no intervention and were only assessed at baseline and at the end of the 24 week period. To evaluate the effect of Botox® treatment in the glabellar region on depressive symptoms the Montgomery-Asberg Depression Rating Scale (MADRS) and the Beck Depression Inventory (BDI) was used. The Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) and Rosenberg Self-Esteem Scale (RSES) was used in the assessment of quality of life and self-esteem respectively. Participants were assessed 3 weeks, 6 weeks, 12 weeks, and 24 weeks after baseline.

In the present study, it was observed that repeated treatments (i.e. two treatments) of Botox® in the glabellar region reduces the symptoms of depression. This effect was observed at the third week and continued until the end of the 24 week follow up period. An 82% vs 21.5% reduction in MADRS scores was observed for the Botox® and placebo group respectively, and only a 16.4% reduction in MADRS scores for the control group. Statistical significant differences (p= 0.001) in MADRS response rates for the treatment groups were observed at week 24. The remission rate at week 24 were 83.3% for the Botox® group. The placebo group had an equal percentage of remission (37.5%) and non-response (37.5%) rates at week 24. It was observed, as depression symptoms improved, there was a simultaneous improvement in quality of life in the experimental group.

Keywords: OnabotulinumtoxinA, Depression, Adjunctive Treatment, Facial Feedback Hypothesis, Self-Esteem, Quality of life, Antidepressant

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Abbreviations

Botox®	OnabotulinumtoxinA
BDI	Beck Depression Inventory
HIV	Human Immunodeficiency Virus
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major depressive disorder
NaCl	Sodium Chloride
Q-LES-SF	Quality of Life Enjoyment Satisfaction Questionnaire – Short Form
RSES	Rosenberg Self-Esteem Scale
SADAG	South African Depression and Anxiety Group
SNAP-25	Synaptosomal Associated Protein -25
SSRI	Selective Serotonin Reuptake Inhibitor
SSNRI	Serotonin Norepinenephrine Reuptake Inhibitors
TCA	Tricyclic Antidepressants

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Chapter 1

Introduction

1.1 Background

Depression is one of the most prevalent mental disorders worldwide. The World Health Organization has established that depression is a key cause of disease burden and disability globally (Whiteford, et al., 2013; Wittchen, et al., 2011). Affecting an approximate 350 million people internationally, depression is coupled with functional impairment, high medical cost, and poor quality of life (World Health Organization, 2011). About 50% of patients diagnosed with depression will respond to antidepressants at the start of treatment and only one in three people will attain remission (Gaynes, et al., 2009).

Depression is a syndrome that can be distinguished by a persistent low mood that lasts for a minimum period of at least two weeks and/or noteworthy anhedonia (World Health Organization, 1992). Additionally, feelings of guilt and low self-esteem, disturbance in sleep and appetite, lassitude and impaired concentration as well as suicide ideation may form part of the clinical symptoms. At least five of the above-mentioned symptoms must be present to corroborate the syndrome. Major Depressive Disorder (MDD) is the most widespread and debilitating form of depression. MDD is characterised by one or more major depressive episodes (APA, 1994). A depressive episode is identified by a time period of at least 2 weeks, where the main symptom is either a depressed mood and/or loss of interest in almost all activities (APA,1994), combined with at least four other symptoms as mentioned above. MDD can be classified as mild, moderate or severe. This is usually dependent on the severity of the symptoms, functional impairment and level of patient distress (Fava & Kendler, 2000). The disorder may result from a complex interaction of several different elements. Namely: genetic epigenetic, environmental and developmental factors. For example, people who have experienced unfavourable life events such as, unemployment, bereavement and psychological trauma are more susceptible to depression (Fava & Kendler, 2000).

The disorder is generally diagnosed by a doctor based on its signs and symptoms. Standardized questionnaires are used to measure the severity of the depression. These are the Hamilton Depression Rating Scale (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS) conducted verbally by an interviewer, and the Beck Depression Inventory (BDI), a self-report questionnaire (Svanborg, & Åsberg, 2001).

Psychotherapy, electroconvulsive therapy, light therapy and pharmacotherapy with antidepressants are presently available for the treatment of MDD. Antidepressants are classified into Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Norepinenephrine Reuptake Inhibitors (SNRIs), Tricyclic and Tetracyclic antidepressants and Monoamine Oxidase Inhibitors (MOA). These are categorised on the basis of their effects on nerve synapses (Fava & Rosenbaum, 1995). Serotonin Reuptake Inhibitors act by preventing serotonin reuptake at the presynaptic nerve terminal. Sexual dysfunction (i.e. delayed ejaculation, anorgasmia, and low libido) are the most common adverse effect of all SSRIs and is said to occur in up to 60% patients (Clayton, Pradko, & Croft, 2002; Massand & Gupta, 2002), and the effects persist as long as the medication is taken. Nausea, diarrhoea, and constipation are the most common gastrointestinal effects experienced. Central nervous system (CNS) effects may include: anxiety, insomnia, sedation (Richelson, 2003; Massand & Gupta, 2002). Tricyclic and Tetracyclic antidepressants were developed soon after monoamine oxidase inhibitors. These antidepressants are rarely used now, because of the availability and accessibility of less toxic and more selective medications (Xhawam, Laurencic, & Malone, 2006). Tricyclic antidepressants (TCA's), inhibits the reuptake of norepinephrine and serotonin. Some of the adverse effects of this drug may include symptoms such as dry mouth, constipation, urinary retention, blurred vision, confusion and delirium. Cardiovascular side effects may include tachycardia and slow cardiac conduction. Slow cardiac conduction may result in intraventricular delay and atrioventricular block (Roose & Glassman, 1989). Sedation is the most common adverse effect of TCAs. Sexual dysfunction and weight gain are also common side effects experienced with TCAs. Monoamine Oxidase Inhibitors (MOA) are another class of antidepressants, these drugs work by irreversibly inactivating monoamine oxidase in the central nervous system, platelets, liver and gastrointestinal tract, the latter of which may cause tyramine absorption. These antidepressants are very effective, but dietary limitations and the possibility of hypertensive crises restrict their use. Side effects may include: reflex tachycardia and dizziness this may be caused by postural hypotension (most common side effect), weight gain, sedation, a severe increase in blood pressure - this is usually activated by ingesting food that is rich in tyramine or sympathomimetic drugs.

1.2 Botulinum Toxin

Botulinum toxin is a protein and neurotoxin synthesized by the micro-organism *Clostridium botulinum*. It is one of the most poisonous biological substances known to mankind (Munchau & Bhatia, 2000). *Clostriduim botulinum* is an anaerobic bacterium usually found in plants, soil, water, and the gastrointestinal tract of animals. The bacterium is mostly known to cause severe food poisoning combined with the rapid onset of paralysis and respiratory arrest (Delcanho, 2009). The therapeutic effectiveness of this neurotoxin was first demonstrated in the treatment of strabismus (Delcanho, 2009). Consequently, Botulinum toxin was accepted for the management

of several other disorders of spasticity, hyperhydrosis, hypersalivation, etc. In 2002, botulinum toxin type A was approved by the Food and Drug Administration (FDA) for the aesthetic use of temporarily reducing glabellar forehead frown lines (Nigam & Nigam, 2010).

Eight antigenically distinct but structurally similar serotypes of Botulinum toxin (A-H) have been recognized, with all serotypes preventing the release of the neurotransmitter acetylcholine. When acetylcholine is not released, muscle contraction is unable to occur. However, they differ in their potency and other biological properties (Nigam & Nigam, 2010). The structure of the toxin can be described as a polypeptide, which comprises of two sub-units, a heavy chain (100-kDa) linked by means of a disulphide bond to a light chain (50-kDa) (Dressler & Adib Saberi, 2005). The afore-mentioned toxin function at four sites in the body. These are: the neuromuscular junction (NMJ), autonomic ganglia, postganglionic parasympathetic nerve endings, and postganglionic sympathetic nerve endings that release acetylcholine (Sellin, 1985).

1.2.1 Mechanism of Action

In normal conditions, acetylcholine disseminates into the synaptic cleft at the neuromuscular junction (NMJ) to attach to acetylcholine receptors on the motor end plate of the muscle cell. When acetylcholine binds to its receptors, it initiates an increase in the opening of the sodium and potassium ion channels which in turn causes depolarization of the motor end plate and muscle contraction occurs. When the toxin is injected in the muscle, it acts at the NMJ to cause muscle paralysis by blocking the release of acetylcholine from presynaptic motor neurons. The heavy sub-unit of the toxin has a high affinity for receptors located on the terminal membranes of cholinergic neurons. The process starts when the heavy chain selectively and irreversibly bind to receptors, this creates a toxin-receptor complex, which undergoes endocytosis. The disulphide chemical bond between the two sub-units is split and the toxin is released in the cytoplasm of the neuron. The enzymatic component of the toxin (light chain) interacts with synaptosomal associated protein (SNAP-25), vesicle associated membrane protein, and syntaxin on nerve terminals. The light subunit of the toxin blocks acetylcholine by proteolysis of SNAP-25, which results in a decrease concentration of acetylcholine released at the synaptic cleft, causing inhibition of its exocytosis. A lack of acetylcholine receptors at the motor end-plate, is followed by a decline of neuronal activity in the target organ, and this ultimately results in muscular denervation. Thus, this toxin, interrupts a crucial step in the process of skeletal muscle contraction resulting in temporary muscle paralysis (Dressler & Adib Saberi, 2005). The peak of the paralysis on the muscle occurs approximately four to seven days after injection. Muscle function is restored by the sprouting of nerve terminals and the formation of new synaptic contacts. This often takes approximately 2-3 months to occur (Nigam & Nigam, 2010). Botulinum toxin has been shown to have no direct

effects on the central nervous system as it is unable to pass through or penetrate the blood-brain barrier.

1.2.2 Clinical Applications of Botulinum Toxin A

Botulinum toxin A has been proven to be effective in treating a wide range of disorders such as cervical dystonia, lower back pain, benign prostatic hyperplasia, incontinence, overactive bladder, spasticity associated with Parkinson's disease and many other medical conditions. Recently, it has been used as a treatment in Tourette's syndrome. Botox® has been used to treat children with cerebral palsy to relax their muscles and to help them walk. The results of the treatment for painful conditions such as the aforesaid led scientists to investigate its use for other painful conditions, such as headaches and migraines. One of the most therapeutic uses of Botox® is to alleviate pain. There are three mechanisms by which Botox® alleviates pain in painful disorders. The first mechanism is to interrupt neuromuscular transmission, this inhibits the release of acetylcholine. In doing so, it prevents the contraction of the muscle spindle, which in turn inhibits the pain-spasm cycle and relieves the person from a painful posture (Arezzo, 2002). The second mechanism is where Botox® has an effect on SNARE proteins to decrease the release of pain mediators. This includes glutamate, substance P and Calcitonin gene related peptides (CGRP) (Bentsianov, Francis, & Blitzer, 2004). This effect can be achieved by blocking the release of substance P from the trigeminal sensory afferent terminal and CGRP from the autonomic vascular nerve terminals (Sheann, 2002). The third mechanism uses a combination of Botox® and lectin for pain relieve without paralysis and it is applied to the posterior root ganglia. In this method, Botox® selectively influences nociceptive sensory afferents, C fibers, and may reduce nociceptive transmission *in vitro* and *in vivo* for a minimum of 24 days (Sheann, 2002).

Table 1.1: Clinical Applications of Botox®

Indication	Description	Effect of Botox®	Reference
Upper Motor Neuron Syndrome	Affected muscles are weak and has reduced motor control. Altered muscle tone and decreased ability to extend, some muscles may exhibit an abnormally high (muscle) tone & lack active lengthening which may reduce joint motion.	Reduce its level of muscle contraction, this can allow better reciprocal motion and improved ability to move and exercise.	Esquenazi, et al., 2013
Cervical Dystonia	Chronic neurological movement condition. The head moves involuntarily to the right, left, downward or upward.	Relieve pain & lessening dystonic posturing by working on altering sensory input in the CNS in addition to its effects on the NJ.	Jost, Blümel & Grafe, 2007
Blepharospasm	Irregular contraction or twitch of the eyelids. Essential blepharospasm and reflex blepharospasm.	Inducing localised and partial paralysis.	Kollewe, et al., 2015
Severe Primary Axillary Hyperhidrosis	Excessive underarm sweating.	Localised, long-lasting but reversible decrease in cholinergic transmission.	Swartling, Naver, Lindberg, 2001
Esophageal Achalasia	Incomplete lower esophageal spincter relaxation, increased LES tone, & lack of peristalsis of the esophagus.	Temporarily paralyse the nerves that signal the LES to contract. Thereby helping to relieve the obstruction.	Pehlivanov & Pasricha, 2006
Focal Dystonia	Neurological muscular disorder. Causes involuntary muscular contractions and abnormal postures in affected muscle or group of muscles in a specific part of the body.	Temporarily weaken the muscle, reducing the spasm.	Jost, Blümel & Grafe, 2007
Migraine Disability	Chronic migraine.	Block the discharge of peripheral nociceptive neurotransmitters. This can have a domino-effect on central pain processing systems that cause migraines.	Mathew, et al., 2005
Bruxism	Oral parafunctional habit, characterised by extreme grinding of the teeth and/or extreme clenching of the jaw.	Partially paralyse affected muscles and decrease their ability to excessively grind and clench the jaw, aiming to keep enough muscular function to allow normal activities.	Long, et al., 2012

1.2.3 Aesthetic Applications

Cosmetic indications of Botox® have dramatically increased during the past decade, particularly since it has been approved for the treatment of glabellar frown lines (Nigam & Nigam, 2010). Not too long ago, Botox® was mostly limited to the improvement of muscles for facial expression over the upper region of the face (Dressler, 2012). At present, its applications vary from treatment of facial lines and wrinkles all over the face, chin and neck. Botox® improve facial wrinkles or frown lines by affecting the underlying muscles, which in turn affects the overlying rhytides (Flynn et al., 2003). The toxin has a paralytic effect on the injected muscle such as the corrugator or procerus. However, the toxin's effect is temporary and reversible.

1.2.3.1 Horizontal Forehead Lines

The horizontal lines in the forehead region of the face is caused by the frontalis muscle, it is the simplest area in the face to treat with Botox®. The function of the frontalis muscle is to raise the skin of the forehead and elevate the eyebrows.

1.2.3.2 Lateral Canthal Lines

The lateral canthal wrinkles ("crow's feet") are produced by the *Orbicularis oculi* muscles. Lateral canthal wrinkles are a result of ageing, exposure to ultraviolet radiation or over-activity of the lateral aspect of the muscle, this can be improved by treatment with Botox®.

1.2.3.3 Glabellar Frown lines

The most preferred and common region of the face to treat with Botox® is the glabellar frown lines. The frown lines are produced by four depressor muscles, namely: paired *Corrugator supercilli*, procerus, the supramedial and supralateral portions of the *Orbicularis oculi* (Wieder & Moy, 1998). The function of this group of muscles are to lower the eyebrows and adduct them medially. The paired *Corrugator supercilli* muscles are small and deeply situated, originates from the nasal process of the frontal bone right above the margin of the medial part the orbit, and spreads out laterally and upward. The muscle inserts into the skin just above the middle of the eyebrow. The *Corrugator supercilli* muscles are principally responsible for causing the glabellar frown lines, with added input from the frontalis, orbicularis, and procerus muscles as shown in the figure below (Figure 1.1). The procerus muscle fibers are vertically oriented and it produces the horizontal wrinkles of the glabellar complex and nasal roof. The muscle originates from the bridge of the

nose and the upper region of the upper lateral nasal cartilage. The procerus inserts into the skin of the roof of the nose (Wieder & Moy, 1998).

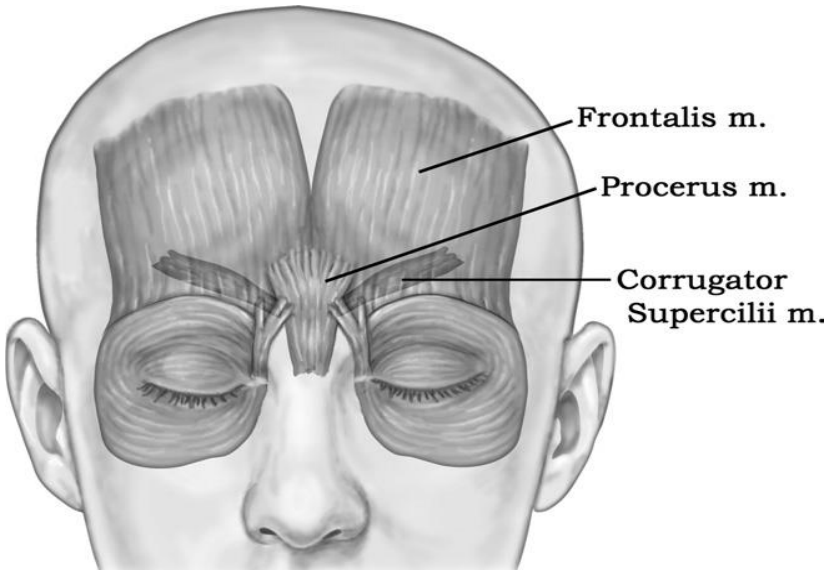

Figure 1.1: Muscular anatomy for glabellar Botox® injections.

1.2.4 Side Effects of Botox®

Side effects are categorized as obligate, local, or systemic. Obligate side effects are defined as natural effects produced by the therapeutic principle of Botox®. Side effects that are caused by the dispersion of Botox® from the target muscle into neighbouring tissues are known as local adverse effects. Systemic adverse effects occur in distant tissues, it is caused by the dissemination of Botox® from the injection site (Dressler, 2012). Although, Botox® has a high affinity to the cholinergic nerve terminal, small quantities of the toxin may be disseminated in the bloodstream. This systemic dissemination can be identified by an increase in neuromuscular jitter in tissues remote from the site of injection (Lange, et al., 1987; Olney, et al., 1988; Girlanda, et al., 1992). Clinically, it is only identified when very high doses of Botox® are used (Dressler, 2012).

However, injections with Botox® are usually well tolerated and adverse effects are minimal and differs with each individual. Side effects that have been reported include: blepharoptosis, diplopia and injection site weakness. The two predominant areas of adverse effects are paralysis of the incorrect muscles and allergic reaction. Local injection site discomfort and bruising are common after injection with Botox®. There can be minimal local swelling, erythma, ecchymosis, transient numbness or headache, malaise or mild nausea (Guyuron & Huddleston, 1994; Garcia & Fulton,

1996; Matarasso, 1998; Carruthers & Carruthers, 1998). Flu-like symptoms and general muscle weakness, breathing and swallowing difficulties (Bakheit, Ward, & Mclellan, 1997) are systemic effects of Botox®. However, it must be noted that these adverse effects are rare and only occur when Botox® is incorrectly administered and patients do not adhere to the post treatment guidelines and take proper precautions.

1.3 Problem Statement

As mentioned earlier, depression is a highly prevalent mental disorder, and it has a considerable social and economic impact in South Africa. Studies have shown that one in 10 South Africans will be diagnosed with Major Depressive Disorder (MDD) at some point in their lives (South African Stress and Health Study). MDD is a potentially debilitating syndrome that affects many realms of the patient's life and results in notable social and occupational dysfunctions. Other negative effects of depression include: suicide, medical morbidity and mortality (Lepine & Briley, 2011). Depression is correlated with a loss in productivity at the workplace (Broadhead, et al., 1990). This means that if an employee is suffering from depression, but is at work, they are 5 times less likely to be productive at work than an employee who was not present due to the condition. A study by HEXOR Pty (Ltd), on the impact of depression at work showed that 54% of people who are depressed said they took more time to do simple tasks, while 50% made more errors than normal at work (Stander, et al., 2016). A 2015 national South African survey conducted by the South African Depression and Anxiety Group (SADAG), indicated that people with depression took an average of 18 days off work due to their depressive illness (Bateman, 2015).

Depression is said to be a cause as well as a consequence of low self-esteem. The disorder profoundly reduces the affected individual's quality of life. Loss in income, arising from workplace absenteeism, reduced productivity or unemployment is a great burden for the affected individual and his/her spouse and family. At a time when the individual is at an enormous need of support, the disorder tends to disturb family stability often resulting in separation and consequently divorce. The association between the condition and divorce can be bi-directional. This means that divorce/separation can either be a cause or consequence of the disorder (Briley & Moret, 2010). Furthermore, troubling side effects associated with current antidepressants are a major reason why most people terminate treatment and subsequently relapse (Finzi & Rosenthal, 2014).

In addition to this, the cost of treating depression is expensive, and involves both direct and indirect costs. Direct costs of treatment include the cost of antidepressants and clinical visits. Indirect cost ranges from decreased productivity at work, absenteeism from employment to early death (Bateman, 2015). From the abovementioned, it can be seen that there is a gap in knowledge for further research on more effective methods in the treatment of depression. With that said, this

study seeks to find a novel approach in the treatment of depression that results in minimal side effects. It will seek to assess whether Botox® injections in the glabellar area can be used in conjunction with current antidepressants, to strengthen the effect of the treatment and provide an overall better prognosis for depression.

1.4 Research Questions

Deriving from the problem statement, the research question is as follows: Does Botox® injections in the glabellar area combined with conventional antidepressants significantly reduce depressive symptoms and does it contribute to higher self-esteem scores and ultimately a better quality of life?

1.5 Research Hypotheses

- Botox® treatment in glabellar frown lines will reduce depressive symptoms.
- Botox® injections in glabellar frown lines can be used as an adjunctive therapy for Major Depressive Disorder.
- Botox® therapy will increase self-esteem scores.
- Botox will reduce depressive scores and leads to an increase in self-esteem and improved quality of life.

1.6 Research Aim and Objectives

1.6.1 Aim

This study aimed to investigate the effectiveness of OnabotulinumtoxinA (Botox®) injection for glabellar frown lines as an adjunctive treatment for Major Depressive Disorder.

1.6.2 Objectives

- To evaluate the effect of repeated treatments of Botox® in the glabellar region on depressive symptoms. This will be assessed using accepted depression rating scales.
  Primary and secondary outcomes measures will be evaluated. The primary outcome measure is a response to treatment, this is defined as a 50% or greater decrease in MADRS scores from the first visit (baseline). Secondary outcome measures include a remission rate, defined by a MADRS score of 10 or lower. An additional secondary outcome measure include a clinical response, observed as changes in the BDI scores at week 3, 6 and 12 post treatment. Clinical response as measured by the BDI can be defined and categorized as:

Response (≥ 50 % reduction in BDI score from Baseline); partial response (25-49% reduction in BDI score from Baseline); non-response (≤ 25% reduction in BDI score from Baseline); remission (BDI score of ≥ 9).

- To determine the effects Botox® injections in the glabellar has on quality of life as assessed by The Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF).
- To measure the effects Botox® injections in the glabellar has on self-esteem as assessed by the Rosenberg Self-Esteem Scale.

1.6.3 Secondary Objectives

- To investigate whether Botox® injections administered in glabellar frown lines augment conventional antidepressant medication.
- To determine if the antidepressant effect of Botox® holds over time.
- To determine whether Botox® injections administered in glabellar frown lines improve quality of life and self-esteem.

1.7 Relevance of the Research

There is data indicating that individuals receiving treatment with Botox® for glabellar frown lines have significantly improved depressive symptoms (Finzi & Wasserman, 2006). However, only a few studies thus far have investigated the effectiveness of Botox® for the treatment of depression. This study seeks to add to existing knowledge on the use of Botox® as an adjunct treatment for depression. It also highlights the use of two treatments of Botox® in the glabellar area over a three month period and what effects it has on depressive symptoms. Furthermore, this is the first study that assessed the therapeutic effectiveness of Botox® in patients diagnosed with depression whilst concurrently assessing the use of Botox® in the improvement of self-esteem scores and how it ultimately affects quality of life.

It is possible that improved productivity at work, increased quality of life and self-esteem are also linked with this treatment (Dayan et al., 2010). Other likely benefits of Botox® treatment for depression include: (I) minimal to no side effects of local Botox® injections into the corrugator and procerus muscles (Brin, et al., 2009); (II) The long-term effect of one dose should help with compliance with conventional medication, which can often be problematic in the treatment of depression (Serna et al., 2010); (III) Due to long-treatment intermissions, it is reasonably cost efficient (Beer, 2010).

1.8 Thesis Outline

This dissertation consists of five chapters: The first chapter introduces the study and provides background information on depression and Botulinum toxin. It also presents the problem statement and research questions the study aims to address. Chapter two provides an extensive literature review on the Facial Feedback Hypothesis and it also critiques studies done on the topic. Chapter three describes the methodology and research design employed to carry out the research. Chapter four presents the statistical analysis of the data. The final chapter discusses the main findings of the study in the light of existing literature and concludes with recommendations for future research on the topic.

1.9 Chapter Summary

This chapter provided a brief background on depression and current antidepressants available for treatment of the disorder. It also examined the side effects associated with each antidepressant class. Furthermore, this chapter defined Botulinum toxin and it's mode of action, as well as its clinical and aesthetic applications. The problem statement is also presented and the rationale for the research is described. The chapter concludes with the aim, objectives and hypotheses of the study. In the next chapter a review of the literature is presented.

Chapter 2

Literature Review

The facial feedback theory is a crucial component of this dissertation, as it attempts to explain a possible mechanism for the effect of Botox® on depression. This chapter reviews previous studies on the facial feedback hypothesis, and examine the influence of self-esteem on depression**.** It will also comment on the comorbidities of depression. Finally, it will review the current literature on the effect of Botox® on depression.

2.1 The Facial Feedback Hypothesis

Charles Darwin (1872) and William James (1890) formulated the facial feedback hypothesis that maintains that facial expressions sends information back to the brain, consequently affecting emotional experiences positively or negatively (Finzi & Rosenthal, 2014). This implies that deliberate contraction of the face muscles into a smile or frown can lead to feelings of happiness or sadness respectively (Soussignan, 2002; Lewis, 2012), affects the emotional assessments of events (Flack, 2006 ; Neal and Chartrand, 2011), and result in particular changes in the autonomic nervous system (Ekman, et al., 1983). The facial feedback theory implicates a mutual interaction between emotional experience and facial muscular activity. This theory predicts two parallel effects: (I) expressing a facial expression should increase the strength of that emotion; (II) inhibiting a facial expression should decrease the intensity of that emotional experience (Alam, et al., 2008). Several researchers have subsequently corroborated aspects of this hypothesis (Strack, et al., 1988; Adelmann and Zajonc, 1989; Larsen, et al., 1992).

A study by Cupchick and Leventhal (1974), showed that when people watched cartoons smiling, instead of frowning, they rated the cartoons as more funny. Also, individuals rated negative/unpleasant images as more aggressive when frowning contrary to smiling. Subsequent researchers criticized these earlier studies, as it was observed that participants were aware of the hypotheses, this may have negatively impacted the results of the study. Successive researchers tried to remove such bias, such that subjects were not aware of the hypotheses.

In an experiment by Strack et al., (1988), study participants were asked to hold a pen between their lips, this was done in order to prevent them from smiling. Furthermore, they were requested to hold a pen between their teeth, this served to promote smiling. Subjects were then required to rate the comicality of the cartoons. It was found that when subjects held the pen between their teeth, they found the cartoons funnier, than those that were restricted from smiling. Therefore, it was

deduced that smiling which is a result of contraction of the *Zygomaticus major* muscle assist in positive decision making. More than a decade later Soussignan (2002) emulated the demonstration of Strack et al., (1988) on the facial feedback effect. However, in his simulation, electromyography (EMG) activity was taken in order to evaluate whether muscle action was being conserved. In this experiment it was found, that a positive expression on the face resulted in a more positive assessment of a stimulus.

Larsen et al (1992) attached golf tees to participant's forehead area. Participants were requested to contract their glabellar muscles in order to produce a frown, in doing so, moving the two golf tees attached to their forehead closer together. This resulted in participants rating negative photographs, more negatively. It was established that frowning, despite of the reason, resulted in a more negative assessment of an unpleasant image (emotional - evoking image) and impacted decision making.

One study compared the effects that different facial expressions have on the autonomic nervous system. Participants were asked to display facial expressions of disgust, fear, anger, surprise and happiness, or to remember an event that triggered these emotions. The findings suggested that blood pressure, heart rate, skin conductance and sweating were influenced more by the contraction of the muscles in the face than by the recollection of an emotional experience (Ekman, et al., 1983).

Several studies have arrived at the same conclusion, using various different methods to control facial expressions. Adelmann and Zajonc (1989) studied the use of the German vowel "u". This was done to prevent subjects from smiling whilst concurrently producing a frown. Native German speakers were requested to read two narratives audibly. Both stories comprised of multiple words containing the "u" vowel, whilst the other story contained none. Participants evaluated the stories on multiple criteria including which story they liked better or preferred more, indicating that frowning negatively impacts emotion based decision- making.

Mori and Mori (2007) suggested that feedback from facial musculature may also possibly arise from passive cutaneous sensation on the face. It was hypothesized that if a drop of water flows down from a person's cheek, the sensation of it may feel similar to actual crying. To simulate smiling a small drop of water was pipetted near the lacrimal duct, allowing the water to flow down the medial side of the cheek. Subjects were given a false tearing up experience, they were then required to report on how they felt after the experience. It was concluded that a feeling of sadness is elicited, when subjects' felt the cutaneous sensation of tears dropping, even if simulated by means of a water drops flowing down their cheeks (Mori and Mori, 2007). In a subsequent study by Mori and Mori (2009), it was postulated that if the persons' cheeks are raised up, a subjective emotion of happiness will consequently be experienced. Bandages (adhesive) fastened with elastic bands were assembled and applied to lift or depress the cheeks, this was done to simulate smiling

or sadness respectively. Results from this experiment supported the theory, individuals may feel happy when their cheeks are raised up (a simulation of smiling), even in an unnatural way. It was also proven if a persons' cheeks are depressed in a downward direction (simulation of sadness), people may feel sad.

Dimberg and Soderkvist (2011), investigated the voluntary facial action method, in their experiment subjects' were commanded to contract their *Zygomaticus major* muscle (smile) or the *Corrugator supercilli* muscle (frown) when shown different stimuli. It was found that subjects graded the stimuli more positively when smiling as compared to frowning. The results showed that the method successfully produces facial feedback effects.

2.1.1 Proposed Mechanism of the Facial Feedback Hypothesis

Tomkins (1962, 1963) proposed a mechanism for the facial feedback cycle in which a stimulus arouses an innate, subcortical emotion which sends motor nerve signals to facial muscles and secondarily, motor and circulatory impulses to the rest of the body, which results in muscular contractions and postural alterations that are transmitted back to the brain. The signals affect consciousness where it is construed as an emotion. In subsequent work, Tomkins (1980) maintained that it is receptors in the skin of the face instead of the facial muscles that are sending information back to the brain. Izard (1971, 1981) also suggested a feedback loop whereby the perception of a stimulus arouses central neural activity in the brainstem, limbic system, and hypothalamus. The hypothalamus then signals the facial musculature, and ultimately feedback from the muscles of the face to the brainstem, hypothalamus, limbic system, thalamus and likely the cerebral cortex establishes the particular emotion that is experienced.

When a person is incapable of expressing an emotion, it may also influence their mood, for example it has been shown that people with facial paralysis exhibit depressive symptoms (Twerski and Twerski, 1986). Van Swearingen et al., (1999) explored the effect of facial paralysis on depression, with specific focus on the impairment of the *Zygomaticus major* muscles which affects the ability to smile. They examined a number of individuals who displayed different degrees of paralysis in the face. It was found that the degree of the depressive illness of these patients was directly linked to the magnitude of their facial paralysis or ability to smile. From this study, it was demonstrated that the absence of positive feedback from facial muscles received from the lack of smiling means that a positive mood is harder to maintain.

In summary, multiple researchers have successfully demonstrated that facial musculature has significant effects on mood or emotional experience: notably, the zygomaticus muscles involved

in smiling, contributes to or intensifies a happy mood, and the *Corrugator supercilli* muscles involved in producing a frown, contributes or increases a negative/sad mood.

2.2 Depression and Self-Esteem

Self-esteem can be defined as a persons subjective assessment of his or her self-worth as an individual (Trzesniewski, Donnellan, & Robins, 2003). Converging lines of evidence has shown that self-esteem and depression are closely related. Various theoretical models have thus been proposed to demonstrate the link between depression and self-esteem. Some of these models are the vulnerability model, scar model and the reciprocal relation model. The vulnerability model states that a low self-esteem increases the risk for depression, which is a person with a low self-esteem is more susceptible to develop depression. This model identifies low self-esteem as a risk factor for depression. There has been strong evidence supporting the vulnerability model (Orth and Robins, 2013). The scar model suggests that low self-esteem is a result or a by-product of depression instead of a cause. Particularly, the disorder is assumed to continually damage self-esteem, even after remission of a depressive episode. In other words, the experience of the disorder may leave behind 'scars' in the person's self-identity that progressively destroy self-esteem over time (Coyne, et al., 1998; Shahar & Davidson, 2003). The reciprocal relation model implies that the vulnerability model and scar model might function concurrently, that is low self- esteem may be a cause as well as a consequence of depression. All of these models have been confirmed in several recent longitudinal studies, a lot of which utilized large sample sizes and advanced statistical approaches, thus increasing the validity of the conclusions (Orth, et al., 2008; Shahar & Henrich, 2010). Noteworthy, functional definitions of depression include low self-esteem as a possible symptom (APA, 2000).

2.3 Comorbidity of Depression

It has been proven that people suffering from chronic diseases have a greater chance for developing depression in comparison to healthy individuals or people unaffected by chronic illnesses (Noel, et al., 2004; Harpole, et al., 2005). Also, individuals diagnosed with depression present significant rates of comorbidity with chronic diseases. The diagnosis of depression by primary health practitioners might be difficult due to the fact that people with specific diseases for example diabetes, may present with similar physical symptoms to those of depression (Wells, et al., 1989). Depression may possibly cause more impairments or disabilities than most other chronic medical illnesses, for example diabetes and osteoarthritis (Hays, et al., 1995). People with depressive disorders generally have concurrent medical conditions such as hypertension, diabetes, arthritis and cardiac problems (Cassileth, et al., 1984; Chapman, et al., 2005; Noel, et al., 2004). The frequency of these chronic medical disorders in patients diagnosed with depression was proven to

be high despite the medical context of recruitment, with an overall percentage varying from 65% to 71% of participants (Wells, et al., 1991). Many mechanisms may give rise to comorbidity. Firstly, Major Depressive Disorder might bring about another disease. For example, cortisol secretion is raised significantly in patients suffering from depression. Cortisol is a glucocorticoid that raises blood sugar levels and therefore contributes to the progression of Type 2 Diabetes (Lustman & Clouse, 2005; Musselman, et al., 2003). Various studies have shown that depressive disorders greatly impact the progression of concurring medical conditions.

In conjunction with diabetes, other diseases and neurological disorders have been linked with an amplified risk for depression. For instance, Fava et al., (1987) have established that Major Depression Disorder are a serious and potentially fatal complication of Addison's disease, hyperthyroidism and Cushing's syndrome.

The existence of chronic medical illnesses such as diabetes, asthma and angina have been connected with decreased health-related quality of life (Bayliss, Ellis, & Steiner, 2005).

2.4 Effects of Botox® on Depression

It has been suggested that OnabotulinumtoxinA (Botox®) administered into brow muscles to treat glabellar frown lines may improve emotional states (Alam, et al., 2008). Sadness, fear and anger which are considered as negative emotions and are common in depression are coupled with the stimulation of the *Corrugator supercilli* and procerus muscles in the glabellar area of the face (Ekman & Friesen, 1978). The paralysis of these muscles suggests that the ability to produce facial expressions of these emotions is considerably reduced. In a study by Lewis and Bowler (2009), subjects who had undergone treatment with Botox® for glabellar frown lines was compared to those who had received other aesthetic treatments i.e. Glycolic peels, laser peels, and Restylane. Subjects were requested to complete the Irritability-Depression-Anxiety Scale (IDAS), and it was concluded that participants that received treatment with Botox® compared to other aesthetic treatments exhibited considerably less negative mood. However, this was an observational study and limitations include a small sample size (n=25), and only females partook in this study. In an investigation by Heckmann et al., (2003), it was found that participants who received Botox® treatment in frown muscles expressed more positive emotions and less negative emotions.
Botox® injected in the glabellar area, forehead and crow's feet of participants to reduce wrinkles for aesthetic purposes, resulted in greater self-esteem and quality of life (Dayan, et al., 2010).

Until now, few studies have investigated the use of Botulinum toxin A for the treatment of major depressive disorder. Finzi and Wasserman (2006) noted that nine out of 10 participants suffering from depression were no longer depressed two months after Botox® had been injected into

glabellar frown lines. However, limitations identified in this study was the small samples size (n=10), lack of controls, as well as the absence of blinding. In a randomized double-blind placebo controlled study, Wollmer et al., (2012) evaluated the effects of botulinum toxin A injection to the glabellar region as an adjunctive treatment of major depression. In this study thirty subjects were randomly assigned to a treatment group (botulinum toxin A, n=15) and placebo (saline, n=15) group. Results indicated that for the duration of the 16 week follow-up period there was a major improvement in the depressive symptoms of the treatment group compared to the placebo group as measured by the Hamilton Depression Rating Scale. There was also an improvement in the Beck Depression Inventory (BDI) scores and Clinical Global Impressions Scale in those treated with botulinum toxin A injections (Wollmer, et al., 2012). In a study conducted by Hexsel et al., (2013), depressive symptoms and self-esteem was evaluated before and after Botox® injections in glabellar frown lines in subjects treated with and without depression. Botox® injections were administered in depressed and non-depressed subjects. The BDI was used to evaluate depressive symptoms before and after Botox® treatment. The Rosenberg Self-Esteem Scale (RSES) (Rosenberg, 1965) was used to evaluate participants' self-esteem before and after the intervention. It was found that in depressed subjects, BDI scores decreased while self-esteem scores increased.

In a more recent study, Finzi and Rosenthal (2014) evaluated the general therapeutic efficacy of Botox® as a treatment for major depression. As in the study of Wollmer et al., (2012), this study used a randomized, double-blind, placebo-controlled design. Subjects received either Botox® or saline injections into the brow muscles as a treatment for major depression. All participants were assessed at three visits (screening, 3 and 6 weeks post interventions) with the Montgomery-Asberg Depression Rating Scale (MADRS), BDI and with the Clinical Global Impressions scale (CGI). This study supported prior research that Botox® treatment in frown muscles may have antidepressant effects in people diagnosed with major depressive disorder (Finzi and Wasserman, 2006; Wollmer, et al., 2012, Finzi, 2013). The following limitations were identified in this study; subjects were only followed for 6 weeks, and there was a delay of nine days after baseline before participants received their injections. It is likely that depression scores changed in the 9 days between baseline and the intervention. Future research should acquire baseline rating, randomize and begin the intervention all on the same day.

Researchers examined the impact of Botox® on mild to moderate depressive symptoms in people suffering from chronic migraine (Boudreau, et al., 2015). They used the BDI II to quantify depressive symptoms at 12 and 24 weeks after Botox® treatment for chronic migraine. Patients reported an improvement in the amount of migraine free days and also a reduction in their depressive scores/symptoms, though it cannot be eliminated that one manifested as a result of the other (Boudreau, et al., 2015). A randomized, controlled study by Magid et al., (2015) further confirmed and extended prior studies, this investigation utilized a cross-over study design, in

which those participants who primarily/originally were randomized to the treatment (Botox®) group (n=11) were given a second injection of saline and those who were in the control (saline) group were crossed-over to the Botox® group after 12 weeks. Given that the muscle relaxant effect of the toxin had not diminished after 3 months (12 weeks) and the notable improvement in depression symptoms persisted or stayed stable, the experiment essentially had a delayed start design, where the treatment group received the Botox® straight away and the control group received it after a delay of 12 weeks. This study had a follow-up period of 6 months (24 weeks), which allowed for long-term observation for those participants in the first treatment group. It was observed, that the clinical improvement in the depression persisted or continued beyond the aesthetic effect of Botox®. The control group (second Botox® group) also displayed a decrease in depressive symptoms after treatment with Botox® (Magid, et al., 2015).

From this review, it was recommended that long-term, randomized, well controlled studies with repeated treatments should be conducted to better assess the effect of Botox® on major depression. It would be significant to evaluate whether the effects hold over time

Table 2. 1: Brief Summary of Literature Review

Author and Year Published	Methodology	Results	Conclusion
Finzi & Wasserman (2006)	(i) 10 subjects diagnosed with major depression. (ii) Evaluated with the BDI before and after treatment with Botox® for glabella frown lines.	(i) 9 out of 10 subjects no longer depressed 2 months after injection with Botox®. (ii) 10th patient had mood improvement.	(i) First reported study on the use of Botox® in the treatment of depression.
Lewis & Bowler (2009)	(i) 12 subjects had Botox® injected to their glabellar frown lines (ii) 13 patients who had other aesthetic treatment (glycolic peels, laser treatment, Restylane) (iii) Mood of Botox® and control group was compared (iv) Participants completed general questionnaire and IDAS.	(i) Botox® group showed significant less negative mood.	(i) Results support facial feedback hypothesis (ii) Treatments that inhibit frowning correlates with less negative mood.
Davis, et al., (2010)	(i) Treatment group (n=33) received Botox® and control group (n=35) received restylane to frown muscles. (ii) Session 1 (before treatment): participants watch negative, mildly positive & positive video clips, completed filler questions, BDI, PANAS (iii) Session 2 (after treatment) exactly the same procedure as session 1.	(i) The treatment group showed an overall decrease in the strength of emotional experience.	(i) The facial feedback may affect emotional experience.
Finzi & Rosenthal (2014)	(i) 85 subjects who had major depression randomized to receive either Botox® or placebo (saline) injections into corrugator and procerus muscles (ii) Subjects evaluated at screening, 3 & 6 weeks after treatment (iii) Completed MADRS, CGI, BDI.	(i) MADRS scores of the Botox® group reduced to 47% compared to 21% for the placebo group.	(i) Single treatment of Botox® to the glabellar muscles induces significant and sustained antidepressants effects.
Wollmer, et al., (2012)	(i) 30 participants who were diagnosed with depression. (ii) 15 patients received Botox® to glabella frown line (iii) Control group receive placebo injections to frown lines.(iv) Completed HAM-D, BDI, CGI.	(i) Significant improvement in the treatment group was observed 6 weeks after a single treatment compared to placebo group. (ii) Indicated by HAM-D (iii) Improvement in BDI	(i) Single treatment of Botox® to the glabellar region alleviates depression in patients with major depressive disorder.
Magid, et al., (2015)	(i) 24 week, RCT, cross-over study design (ii) 30 participants – Botox® group (n =11), Control group (n = 19). (iii) HAM-D 21, BDI, PHQ-9 (iv) patients evaluated at 0, 3, 6, 12, 15, 18, 24 weeks	(i) Botox® group decrease in symptoms as compared to control group.	(i) Further support Botox® as a treatment for depression.

2.5 Chapter Summary

This chapter reviewed the facial feedback hypothesis and its proposed mechanisms. It also looked at the impact of depression on self-esteem and vice versa. This chapter also summarised the major comorbidities of depression. Furthermore, this chapter reviewed the existing literature on the effect of Botox® on depression.

Chapter 3

Research Methodology

3.1 Research Design

This study utilized a randomised, placebo-controlled design in which standardized and validated questionnaires were used to collect quantitative data on patients. The dependent variables in this research were depression, quality of life, and self-esteem. The intervention used was the treatment of subject using Botox®. Thus, Botox® was the independent variable.

An initial sample size calculation yielded a result of 54 participants for which 18 participants per group would have been allocated (Botox® group: n = 18; placebo group: n = 18 and control group: n= 18. This was based on a difference in mean MADRS scores of 7.7 at 5% significance and a power of 80% (Finzi & Rosenthal, 2014).

In total 54 participants were assessed for eligibility into the study. Twenty-seven patients were lost to follow-up and excluded: 5 patients in the Botox® group, 5 in the placebo group and 7 in the control group. All 17 patients were lost to follow-up (i.e. they dropped out) which resulted in them not having complete data and they were subsequently excluded from the data analysis. Three patients with HIV were excluded initially. Five patients who did not want to receive Botox® injections were excluded. Two patients was excluded for protocol violation (i.e. discontinued their antidepressant medication).

Twenty seven (27) participants were randomly assigned to either the treatment group (Botox®, n= 12), placebo group (saline, n= 8) and the control group (n = 7). Participants in the treatment group or placebo group were injected with Botox® and saline solution respectively in their Procerus and *Corrugator supercilli* muscles. The control group received no intervention and were only assessed at baseline and at the end of the 24 week period. Female participants received 29 units of Botox®, whereas males received 39 units. The reason why more units of Botox® were given to the male participants is because a greater average corrugator and procerus muscle mass are found in males. A qualified medical doctor trained in Botox® treatment was assigned the task of administering the Botox® and saline injections to all participants. Participants in the treatment and placebo group received two interventions at baseline and 12 weeks after baseline and were followed-up for a period of 24 weeks. All participants, excluding those in the control group were required to come for follow up visits at week 3, week 6, week 12, and week 24. During all follow–up visits, depressive symptoms were evaluated using the Beck Depression Inventory (BDI) and the Montgomery Depression Rating Scale (MADRS). Quality of life and self-esteem level was also

assessed by means of the Quality of Life Enjoyment Satisfaction Questionnaire Short form (Q-LES-SF) and the Rosenberg Self-Esteem Scale (RSES) at follow-up visits.

3.2 Research Setting

The study took place at the University of the Western Cape. All participants were from the Cape Town metropolitan area.

3.3 Participants and Sampling

The participants in the study included 27 adult patients diagnosed with major depressive disorder. The study sample comprised of 7 males and 20 females (this demonstrates a male to female ratio of 1:3). Participants were recruited through advertisements placed in local newspapers (Die Tygerburger 12/10/2016 and 01/03/2017), via flyers, and a Facebook page. The method under investigation (Botox® treatment) was not openly stated during the recruitment process. This was to avoid attracting participants who were mainly motivated by receiving this treatment for aesthetic benefits of Botox®. In order to be eligible to participate in the study, patients were required to have a MADRS score of ≥7.

3.3.1 Inclusion Criteria

Only men and women aged 18-65 years and diagnosed with ongoing major depressive disorder were included in the study. Study participants had to be on at least one antidepressant agent prescribed by a psychiatrist and should have been taking the medication at a stable dosage for at least two months prior to the intervention. Participants were requested to leave their medication unchanged for the duration of the study. Study participants had to be Botox® naïve before the study.

3.3.2 Exclusion Criteria

Participants were excluded if they had prior treatment with Botox® in the glabellar region. Also, patients were excluded if they displayed signs of suicide risk, had a history of substance abuse or dependency in the two months prior to the intervention. Furthermore, exclusion criteria also included conditions that contraindicated the use of Botox®. If patients had been treated with any procedure that might have affected the action or outcome of Botox®, had any neurological or muscular disease, or severe MDD with psychoses they were excluded from the study. Patients with Human Immunodeficiency Virus (HIV) was also excluded due to the risk active infections present

in the affected individual. HIV also causes depression. Depression is found to be the most common comorbid disorder in adults living with HIV or AIDS (Myer, et al., 2008)

3.4 Preparation

This section describes how Botox® and the placebo was prepared for injection in the glabellar area.

3.4.1 Botox®

The Botox® was purchased from Allergan Pharmaceuticals (Pty) Ltd. The 100 unit vial of Botox® was reconstituted with 1.0 ml of 0.9 % Sodium Chloride (NaCl). The Botox® was prepared by an independent researcher. Injections were made using insulin syringes with 30 gauge (12 mm) needles at five specific injection points into the Corrugator and procerus muscles.

3.4.2 Placebo

The placebo group received 0.9 % Sodium Chloride (NaCl) injections in the glabellar area. Syringes prepared for Botox® and placebo group were optically indistinguishable from each other.

3.5 Glabellar Injection Sites

The 0.29 ml total injection volume (29 units) for females was separated into five injections: 0.07 ml (7 units) in the procerus muscle, 0.06 ml (6 units) in the medial part of the corrugator muscle, and 0.05 ml (5 units) in the middle part of the corrugator muscles. Higher dosages of Botox® were given to male vs female patients (39 vs 29 units).

3.6 Randomization and Blinding

All participants were randomly allocated to either group in blocks of 3. Syringes were prepared by a research assistant who had no contact with the participants. As it was a double-blind study, both medical doctor, administering the injections and participants were blind to treatment allocation.

3.7 The Procedure

Study participants were recruited via (i) advertisements in local newspapers (Die Tygerburger 12/10/2016 (Appendix A) and Die Tygerburger 01/03/2017 (Appendix B); (ii) flyers were handed out in the community, at local Doctor's offices/surgeries and local pharmacies (Appendix C); (iii) a Facebook page was created and specifically designed to recruit potential participants. At

baseline/screening, potential participants were briefed about the study and informed about the benefits of their contribution to the study. This information was also provided in the information sheet (Appendix D) which was handed out to participants.

Participants who agreed to take part in the study were provided with consent forms (Appendix E) and required to give written informed consent before the study commenced. Demographic data was collected by means of demographic questionnaires (Appendix F), this questionnaire also gathered information on medical history and current treatments of participants. A trained researcher and clinician carried out the assessments with the Montgomery Depression Rating Scale (MADRS). Patients were then requested to complete the Beck Depression Inventory, Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form and the Rosenberg Self–Esteem Scale. A research assistant was available throughout the data collection process in order to provide assistance and ensure the smooth flow of the research process. A room was located at the UWC (Life Sciences Building) for the participants to complete the questionnaires. This room also warranted that participants had a private space in which to partake in the study. The questionnaires took approximately 30-45 minutes to complete. Participants were randomly assigned to either the treatment, placebo or control group. A standardized photograph was taken of the glabellar at rest and at maximum frowning, and was taken at baseline and at all subsequent visits. At baseline, the first intervention was given in the glabellar region (refer to glabellar injection sites). Following injections, post-treatment rules were explained verbally by the medical doctor and all participants received a hard copy of the post treatment rules. Participants' subsequent appointment schedules was also given at screening. Patients were requested to come for follow-up visits at 3 weeks, 6 weeks, 12 weeks, and 24 weeks after the baseline visit. At each follow-up visit patients were evaluated with the following instruments: (i) MADRS (Appendix G), (ii) BDI (Appendix H), (iii) RSES (Appendix I) and (iv) Q-LES-S (Appendix J). At twelve weeks after baseline, patients received intervention II. Patients did not have contact with each other, all patients were assessed and treated individually. No remuneration or compensation for participation was provided. The study was carried out in an ethical manner, as declared in the section on ethical considerations.

3.8 Ethical Considerations

Ethical clearance was sought and obtained from the University of the Western Cape Faculty Board Research and Ethics Committee, and from the UWC Senate Research Committee (Ref. Code:15/6/92). At screening, participants were briefed and made aware of the nature of the study. Researchers informed participants of the procedure of the study, the duration of the study and the benefits. Prospective participants were made aware that their real names would not be included on any data collection sheets. Each participant signed a consent form before the study commenced. Patients were assigned a participant identification number in order to ensure anonymity and

essential steps were taken to guarantee confidentiality. All information collected i.e. questionnaires and files were locked in filing cabinets and computers that were password protected, information was only retrieved for the purpose of data analysis. Patients were informed that participation is voluntary and that, if they so wish, they could withdraw at any stage during the research process, they would not be penalized or lose any benefits. The experimental treatment (i.e. Botox®) were non-invasive and therefore presented the participant with minimal risks. Participants were not advised to discontinue or change their current antidepressant medication for the duration of the study.

3.9 Data Collection Questionnaires

A series of accepted and validated questionnaires was utilized to collect data from patients. These included a biographical questionnaire, the MADRS, BDI, Q-LES-SF, and the RSES. The biographical questionnaire collected information at baseline about the age, sex and socio-economic/employment status of patients. Medical history with regards to date of first diagnosis of depression, current antidepressants, other medical conditions and medication was also obtained. This information was gathered and used to gain a better understanding of patients and also assessed for comorbidities. To evaluate depressive symptoms, the MADRS and BDI was used. To assess self-esteem and quality of life the RSES and Q-LES-SF was used respectively**.**

3.9.1 The Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS is a 10-item clinician administered measurement tool intended to be principally sensitive to antidepressant treatment effects in subjects diagnosed with Major Depression Disorder. The MADRS also assess for depression severity as well as treatment response. The items are graded on a 0-6 scale (0 = no abnormality, 6 = severe). It took about 15-20 minutes to complete (see appendix G).

3.9.2 Beck Depression Inventory (BDI)

The BDI was used to assess depression severity and response to treatment. The questionnaire comprises of 21 questions established to examine the level, intensity, depth and degree of depression in people from the ages of 13 years and older. The BDI is a self-report measure, hence patients completed it on their own. A research assistant trained in the administration of the questionnaire was on standby, to help if they required any assistance. The BDI took approximately 5 to 10 minutes to complete. Severity of depression based on the BDI is classified into 5 groups: Normal, mild mood disturbance, borderline clinical depression, moderate depression, severe depression, extreme depression (Beck, Steer & Brown, 1996). The 21-items on the questionnaire

produces a maximum total score of sixty-three. Each question has a range of scores from 0 to 3 (Beck, Steer & Brown, 1996) (see appendix H).

3.9.3 Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-S)

The Q-LES-S is a validated self-report measurement tool. It is used to gather information on the level of enjoyment and satisfaction experienced by individuals in several aspects of daily functioning. The instrument consists of 16 items and questions are rated on a Likert scale from 1-5. The minimum raw score is 14 and the maximum 70. The total of the raw score is converted into a percentage score using a formula (see appendix G). The questionnaire takes approximately 5 minutes to complete (see appendix J).

3.9.4 Rosenberg Self-Esteem Scale (RSES)

This RSES is an accepted measurement tool that measures global self-worth. It comprises of a 10-item scale categorised on a 4-point Likert scale which ranges from strongly agree (1) to strongly disagree (4). A score lower than 15 is indicative of a low self-esteem, and scores. This scale has been described as beneficial in measuring self-esteem in adults with or without mental illness' and has been used to evaluate results of plastic surgery and other queries of self-esteem (see appendix I).

3.10 Data Analysis/Statistical Analysis

The data collected was analysed using the Statistical Package for the Social Sciences version 24.0 (SPSS). Descriptive statistics for continuous variables and frequencies for categorical variables was calculated and analysed. Descriptive statistics was used to organise and summarise the data. The Chi-square test was applied to assess response to treatment (i.e. association between categorical variables) as measured by the MADRS and BDI. Two-way analyses of variance (ANOVA)/mixed model ANOVA for repeated measures was used with factors group (Botox® and placebo) and time points, throughout the 24-week follow-up period. Test results with an alpha-level (p-value) ≤ 0.05 was flagged as significant.

3.11 Chapter Summary

This chapter outlined the methodology used to execute the research. It described the research design and setting. Also, it describes the eligibility criteria of participants and the methods used to recruit participants. Furthermore, it defines the procedure used to carry out the study, the data collection tools and ethical considerations. Chapter 4 presents the results of the study.

Chapter 4
Results

4.1 Introduction

The main results of the study are presented in this chapter. The characteristics of the study population at baseline will be described. This includes descriptive statistics of the demographic variables, depression severity of the treatment, placebo and control group as measured by the MADRS and BDI at screening. Also, the quality of life and level of self-esteem of all three groups at baseline is outlined. Furthermore, the primary and secondary outcome measure i.e. response to treatment is described, and the time effect profile of the treatment on depression, self-esteem and quality of life was analysed using Two-way Analysis of Variance (ANOVA) for repeated measures. Finally, the effect of the MADRS and the BDI depression scores on RSES (Self-Esteem) and QLES (quality of life) is evaluated.

4.2 Characteristics of the Study Population

In Table 4.1, the demographic profile of the study population is presented. The sample comprised of 27 adults diagnosed with Major Depressive Disorder. The treatment group comprised of 12 participants, the placebo group consisted of 8 participants while the control group had 7 participants. The males represented a minority of the sample (26%), while the females represented 74% of the total sample. Fifty-six percent of the study population was within the age group of 25-49 years, while 44% were over the age of 50 years. As seen in Table 4.1, 48 % of patients in the study suffered from no other medical conditions, whilst a total of 44% suffered from hypertension. Within the sample, 48% of the sample were unemployed, 41% held regular jobs, 7% were pensioners and 4% were students. A large majority of the sample used a Selective Serotonin Reuptake Inhibitor (SSRI) (88%), whilst only 5% of the study population used Selective Norepinephrine Reuptake Inhibitors (SNRI). In the sample population 37% of participants suffered from MDD for less than 5 years while 26% of patients suffered from depression for more than 20 years.

Table 4.1: Demographic Data of the Study Population

Demographic Variable		Frequency	Percentage
Intervention	Control	7	26%
	Placebo	8	30%
	Botox®	12	44%
Gender	Males	7	26%
	Female	20	74%
Age Group	25 - 49 years	15	56%
	Over 50 years	12	44%
Employment Status	Working	13	48%
	Unemployed	11	41%
	Pensioner	2	7%
	Student	1	4%
Antidepressant Type	SSRI	24	88%
	SNRI	2	7%
	TCA	1	4%
Medical Conditions	None	13	48%
	Hypertension	12	44%
	Anxiety	1	3.7%
	Arthritis	1	3.7%
Duration of MDD	Less than 5 years	10	37%
	6 - 10 years	4	15%
	11 - 20 years	7	26%
	More than 20 years	6	22%
	Total	**27**	**100**

4.4 Primary and Secondary Outcome Measures

The first objective of the study was to evaluate the effect of repeated treatments of Botox® injection in the glabella region on depressive symptoms. This was achieved by assessing whether there were changes in the MADRS scores at 3, 6, 12 and 24 weeks post-treatment. The primary outcome measure was a response to treatment. This was defined as a 50% or greater decrease in MADRS scores from the first visit (baseline).

Secondary outcome measures included a remission rate, defined by a MADRS score of 10 or lower. An additional secondary outcome measure included a clinical response, observed as changes in the BDI scores at week 3, 6 and 12 post treatment. Clinical response as measured by the BDI was defined and categorized as shown in Table 4.2

Table 4.2: Definition of Clinical Responses as Measured by the BDI

Clinical Response	**Definition**
Response	≥50 % reduction in BDI scores from baseline
Partial Response	25 - 49 % decrease in BDI scores from baseline
Non-Response	≤ 25 % reduction in BDI scores from baseline
Remission	BDI score of ≥ 9

4.3 Severity of Depression at Baseline

In this sample, the Botox® group was defined as the group that received the treatment (i.e. Botulinum toxin-A injections into the glabellar frown muscles). The placebo group received saline injections into the glabellar frown muscles. The control group received no intervention and was only assessed at baseline and at 24 weeks post baseline. Using standardized and validated questionnaires (i.e. MADRS and BDI), depression was categorized into mild, moderate and severe (MADRS), the BDI was categorized into mild, borderline clinical depression, moderate, severe and extreme.

Table 4.3 compares the severity of depression and the level of self-esteem at baseline for the Botox®, placebo and control group. As measured by the MADRS, the majority of the participants in the Botox® group (41.7%) was suffering from moderate depression, while 50% of participants in the placebo group had mild depression at screening. Twenty five percent (25%) of patients suffered from severe depression in the Botox® group. In the Botox® group, 50% of participants displayed a low level of self-esteem, whilst 62.5% in the placebo group displayed a normal level of self-esteem. A total of 57.1% in the control group exhibited a low level of self-esteem as measured by the RSES at screening.

Overall, it was found that participants who had a higher level of depression or more severe form of depression at baseline was in the Botox® group. However, there was no significant difference (p=0.93) between the three groups (Botox®, placebo & control group) and the severity of depression at baseline.

Table 4. 3: Baseline Characteristics of Participants

	Botox® (N=12)		**Placebo (N=8)**		**Control (N=7)**		**(P-Value)**
	N	%	N	%	N	%	
Severity of depression (MADRS)							
Mild	4	33.3%	4	50.0%	3	42.9%	
Moderate	5	41.7%	3	37.5%	3	42.9%	0.93
Severe	3	25.0%	1	12.5%	1	14.3%	
Severity of Depression (BDI)							
Normal	2	16.7%	1	12.5%	2	28.6%	
Mild	0	0.0%	2	25.0%	0	0.0%	
Borderline Clinical Depression	2	16.7%	2	25.0%	2	28.6%	0.46
Moderate	1	8.3%	2	25.0%	1	14.3%	
Severe	3	25.0%	0	0.0%	1	14.3%	
Extreme	4	33.3%	1	12.5%	1	14.3%	
Level of Self-Esteem							
Low	6	50.0%	2	25.0%	4	57.1%	
Normal	5	41.7%	5	62.5%	2	28.6%	0.70
High	1	8.3%	1	12.5%	1	14.3%	
Total	12	100	8	100	7	100	

In Table 4.4, the objective rating scores (mean and Standard Error (SE) of all the measurement scales (MADRS, BDI, RSES and QLES-SF) are illustrated as well as the age and duration of depression of all the three groups at baseline. The Botox® group had a higher mean MADRS score (mean = 26, SE = 3.53) than the placebo (mean =19.75, SE = 3.47) and control group (mean = 20.86, SE = 4.21) at baseline. Correspondingly, the Botox® group demonstrated a greater mean BDI score (mean = 29.6, SE = 4.13) than the placebo (mean = 22.13, SE = 4.73) and control group (mean = 21, SE = 5.7). As measured by the QLES-SF, the control group exhibited a higher quality of life (mean = 49.14, SE = 6.91) than the Botox® and placebo group although none was significant.

Table 4.4: Baseline Objective Rating Scores (Mean) of Participants

	Botox®		Placebo		Control		
	Mean %	**SE %**	**Mean %**	**SE %**	**Mean %**	**SE %**	**Sig.**
MADRS	26.00	3.53	19.75	3.47	20.86	4.21	0.429
BDI	29.60	4.13	22.13	4.73	21.00	5.70	0.370
RSES	15.42	1.96	17.63	1.91	17.29	2.29	0.697
QLES	32.00	4.29	40.63	3.54	49.14	6.91	0.063
Age	45.17	2.77	50.50	3.68	45.57	4.09	0.489
Dur.of MDD	13.58	3.13	14.25	4.54	7.86	2.12	0.437

4.4.1 Response to Treatment as Assessed by the MADRS

4.4.1.1 Response to Treatment at Week 3

In Figure 4.1, the remission and response rate at 3 weeks post treatment were 41.7% (5 of 12) and 33.3% respectively, for the Botox® group. The placebo group had a 62.5% (5 of 8) non-response rate at 3 weeks after baseline. However, no statistically significant differences were observed between the placebo and Botox® group in response to treatment at 3 weeks post treatment (Chi-square (2) = 4.38, p=0.112).

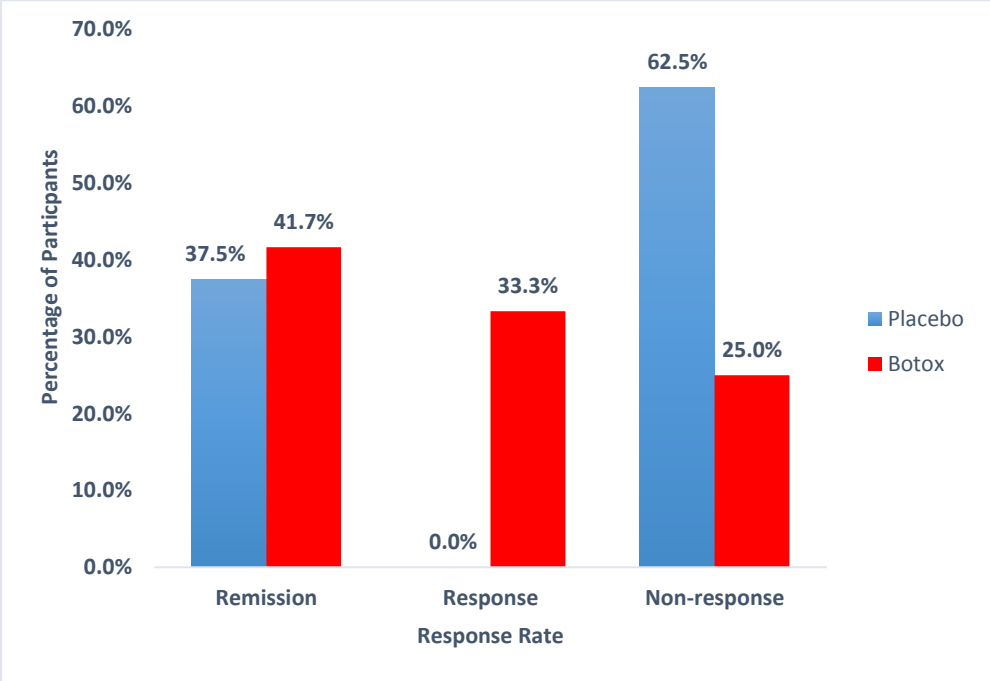

Figure 4.1: MADRS response rates at week 3

4.4.1.2 Response to Treatment at Week 6

In Figure 4.2, the remission rate at week 6 increased to 58.3% (7 of 12) for the Botox® group. There was a non-response rate of 62.5% (5 of 8) and 41.7% (5 of 12) in the placebo and Botox® group respectively (chi-square (2) =3.10, p= 0.212).

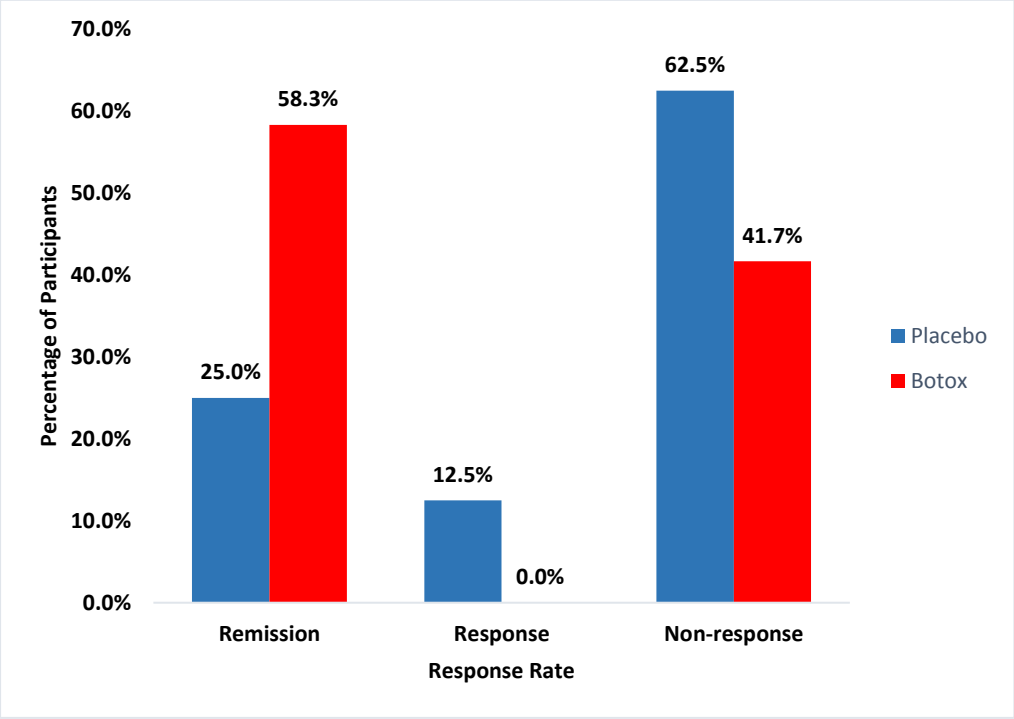

Figure 4.2: MADRS response rate at week 6

4.4.1.3 Response to Treatment at Week 12

As demonstrated in Figure 4.3, a total of 66.7% (8 of 12) participants in the Botox® group was in remission at 12 weeks from baseline. The non-response rate in the placebo group further increased to 75% (6 of 8) at week 12 (Chi-square (2) = 5, p= 0.082).

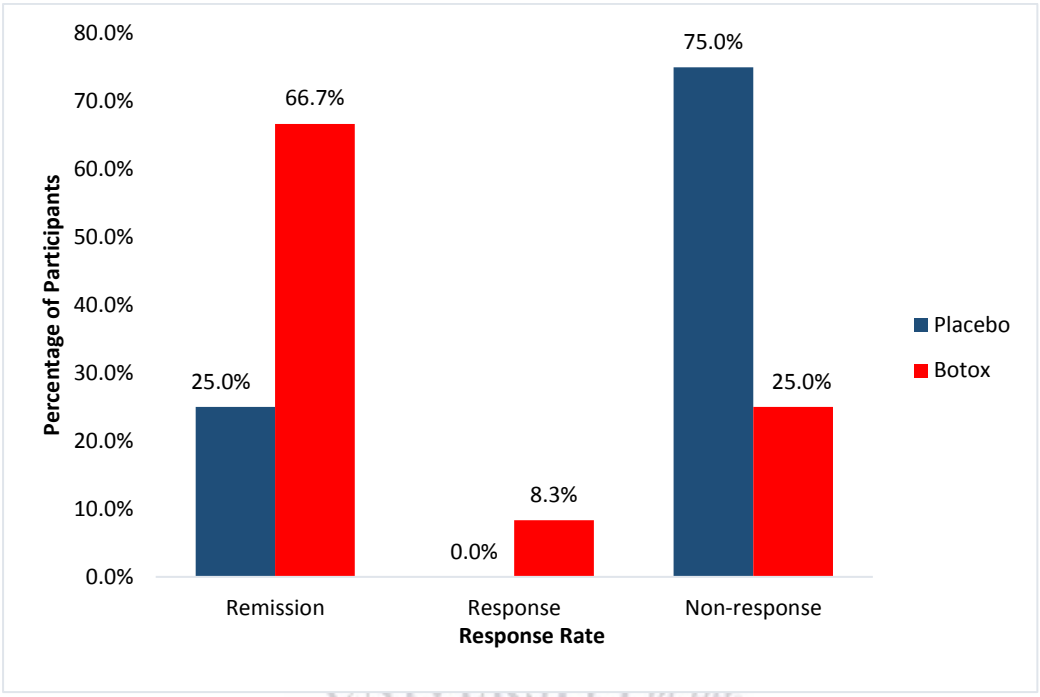

Figure 4.3: MADRS response rate at week 12

4.4.1.4 Response to Treatment at Week 24

As shown in Figure 4.4, statistical significant differences in MADRS response rates for the treatment groups were observed at week 24 Chi-square (4) = 18.04, p= 0.001. The remission rate at week 24 were 83.3% (10 of 12) for the Botox® group. Noteworthy, there was a 100% non-response rate for the control group at 24 weeks from the first visit. The placebo group had an equal percentage of remission (37.5%) and non-response (37.5%) rates.

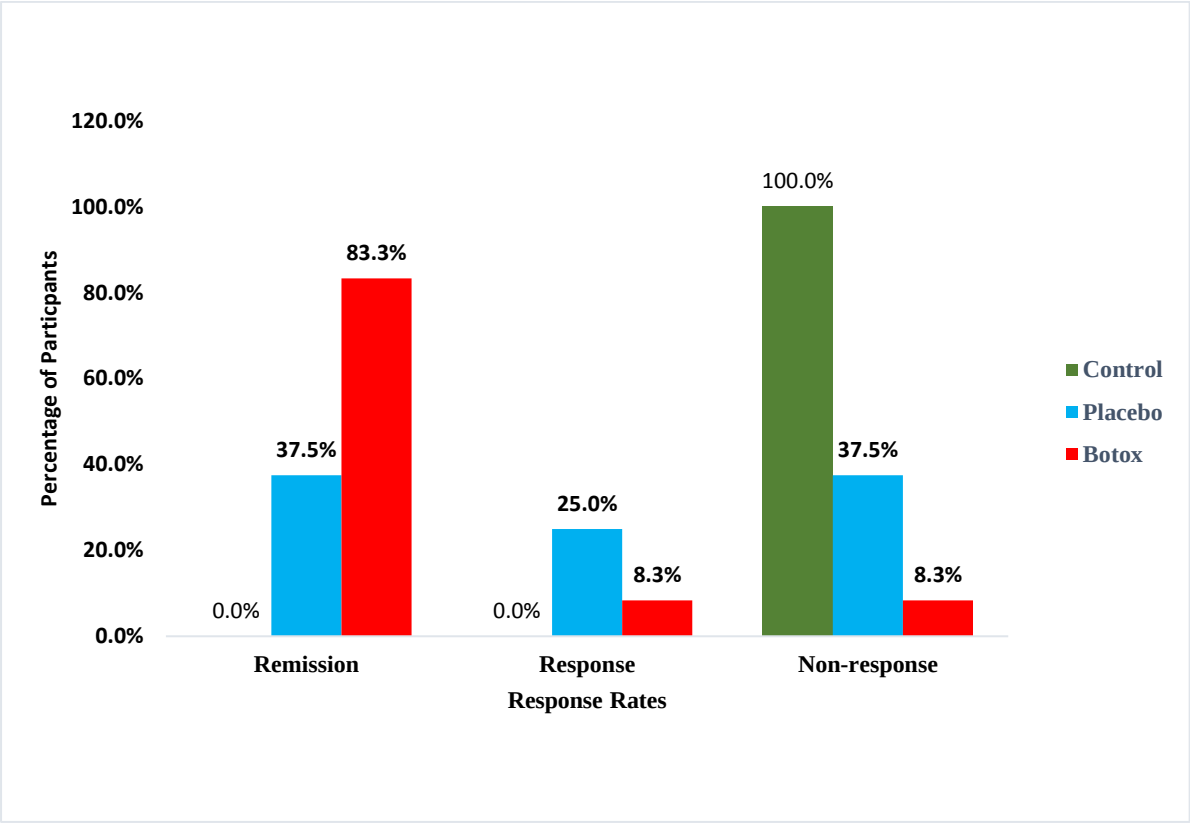

Figure 4.4: MADRS response rate at week 24

4.4.2 Response to Treatment as Assessed by the BDI

4.4.2.1 Response to Treatment at Week 3

As shown in Figure 4.5, the Botox® group had a 41.7% (5 of 12) remission rate 3 weeks after treatment as assessed by the BDI compared to the placebo group which had a remission rate of 12.5%. The Partial response rate were 33.3% (4 of 12) versus 12.5% (1 of 8) for the treatment and placebo group, respectively. Furthermore, the placebo group had a 62.5% (5 of 8) non-response rate at week 3. (Chi-square (3) = 5.16, p= 0.161).

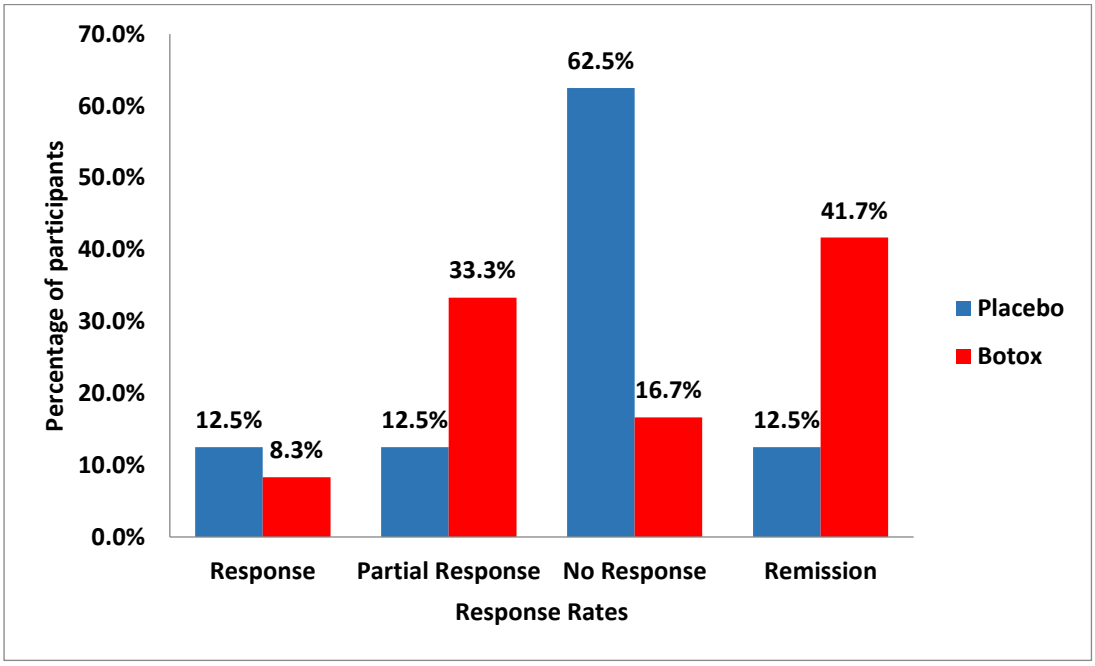

Figure 4.5: BDI response rate at week 3

4.4.2.2 Response to Treatment at Week 6

As displayed in Figure 4.6, at 6 weeks post treatment the remission rate of the Botox® group remained unchanged (41.7%), this group had a partial response rate which was equally the same (41.7 %). Noteworthy, the non-response rate of the placebo group dropped to 50% (4 of 8) and the remission rate increased to 25% (2 of 8). The results were statistically significant (Chi-square (3) = 7.80, p= 0.050).

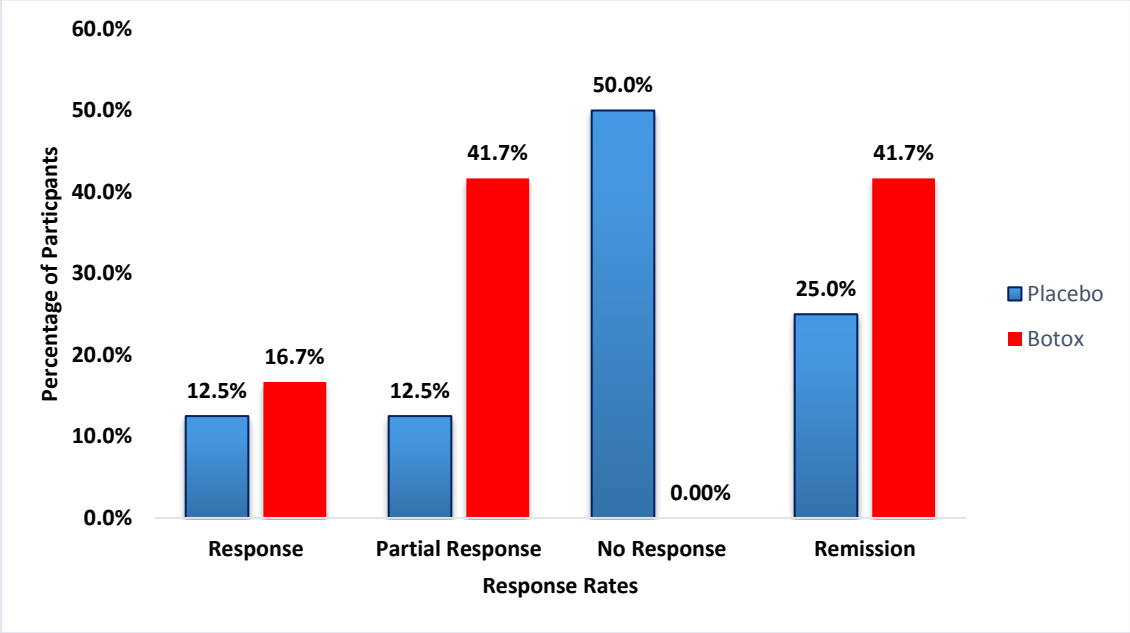

Figure 4.6: BDI response rate at week 6

4.4.2.3 Response to Treatment at Week 12

In Figure 4.7, the BDI remission rate for the Botox® group at 12 weeks post injection were 75% (9 of 12) versus 12.5% for the placebo group. In the latter group the non-response rate was 62.5% (5 of 8). The results were statistically significant (Chi-square (3) = 11.40, p= 0.010).

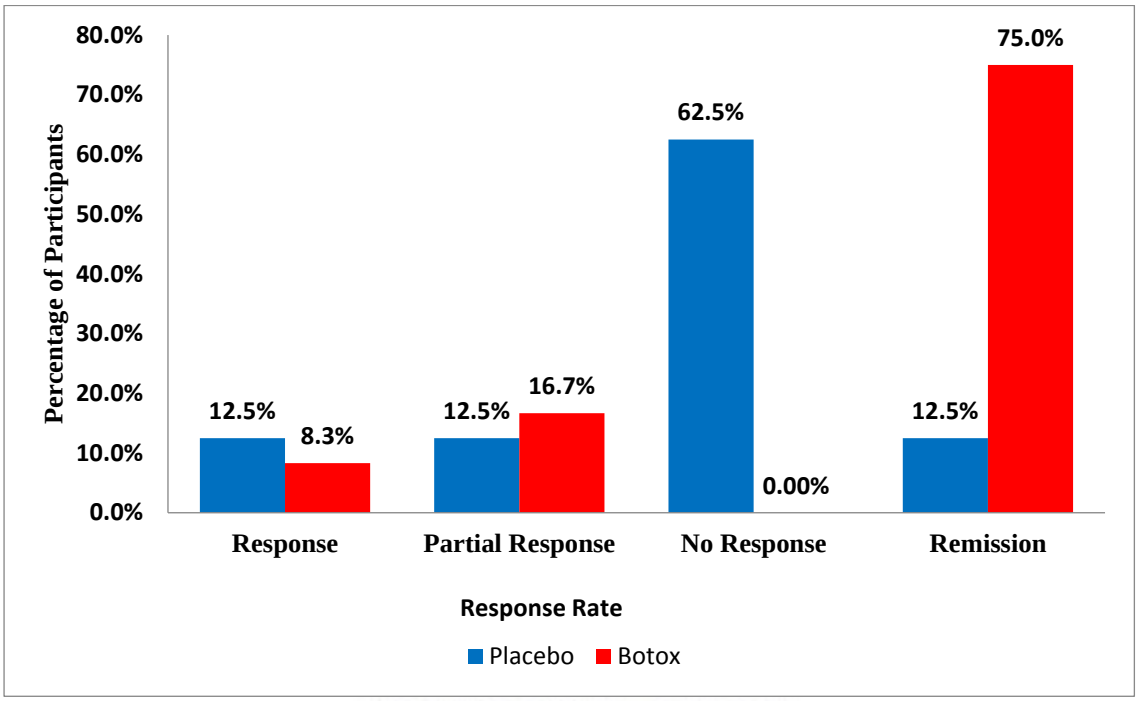

Figure 4.7: BDI response rate at week 12

4.4.2.4 Response to Treatment at Week 24

As shown in Figure 4.8, at 24 weeks from baseline the Botox® group remission rate decreased to 66.7% (8 of 12) and it had a response rate of 16.7% (2 of 12). The remission rate of the placebo group increased to 37.5% (3 of 8). The control group had a non-response rate of 57.1% (4 of 7) and a partial response rate of 28.6% (2 of 7) Chi-square (6) = 11.17, p= 0.083).

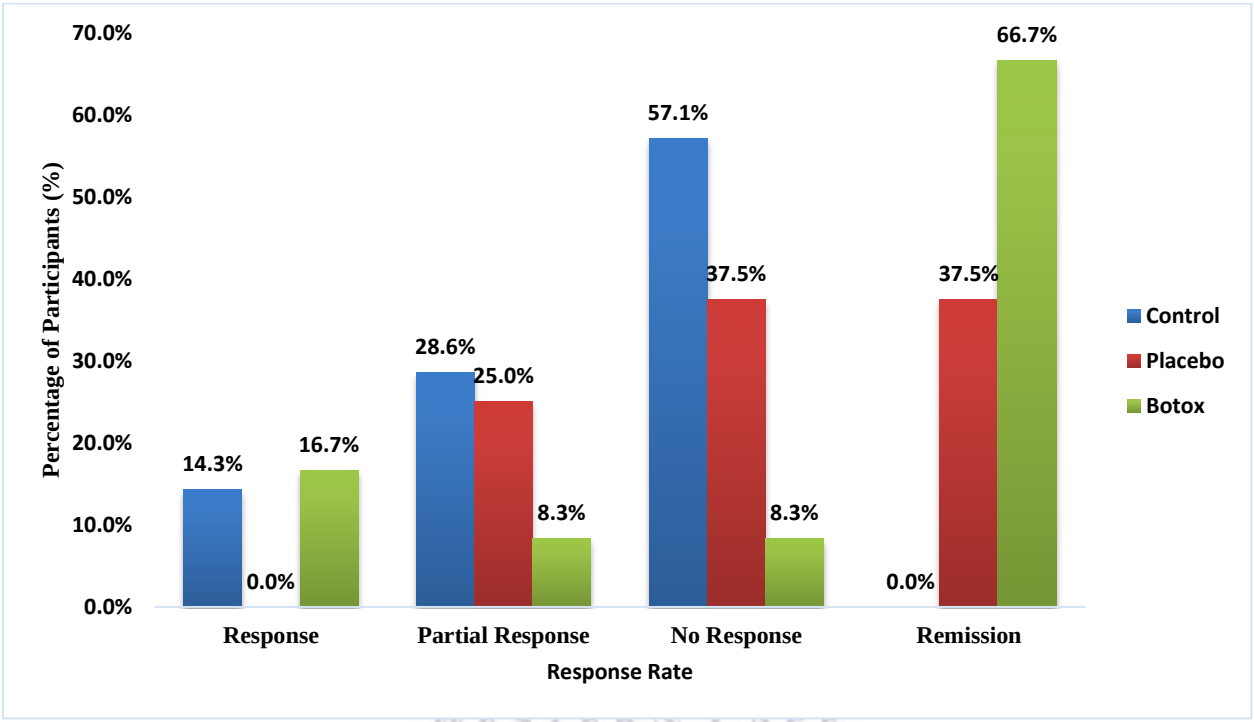

Figure 4.8: BDI response rate at 24 weeks from baseline

4.5 Time Effect of Treatment on Depression

4.5.1 Time Effect of Treatment on Depression as Assessed by the MADRS

The results of the Two-way ANOVA for repeated measures showed that there was a significant main effect of the time (weeks) ($F(4, 72) = 6.62$, $p = 0.000$, $np^2 = 0.27$) on MADRS depression scores overall. From baseline (mean = 22.9, SE = 2.58) the overall MADRS depression scores decreased until week 24 (mean = 10.1, SE = 1.94). However, there were no significant main effect ($F(1, 18) = 1.89$, $p = 0.186$, $np^2 = 0.09$) observed on MADRS depression scores overall between the two different groups (Botox® and placebo group).

In contrast, there was a significant interaction between time and the two different groups ($F(4, 72) = 3.72$, $p = 0.008$, $np^2 = 0.09$) in terms of MADRS depression scores. Figure 4.9 shows that for the Botox® group, the mean MADRS depression scores continued to decrease consistently from the first visit until week 24. It also shows that the placebo group mean MADRS scores decreased at week 6 and subsequently increased again at week 12.

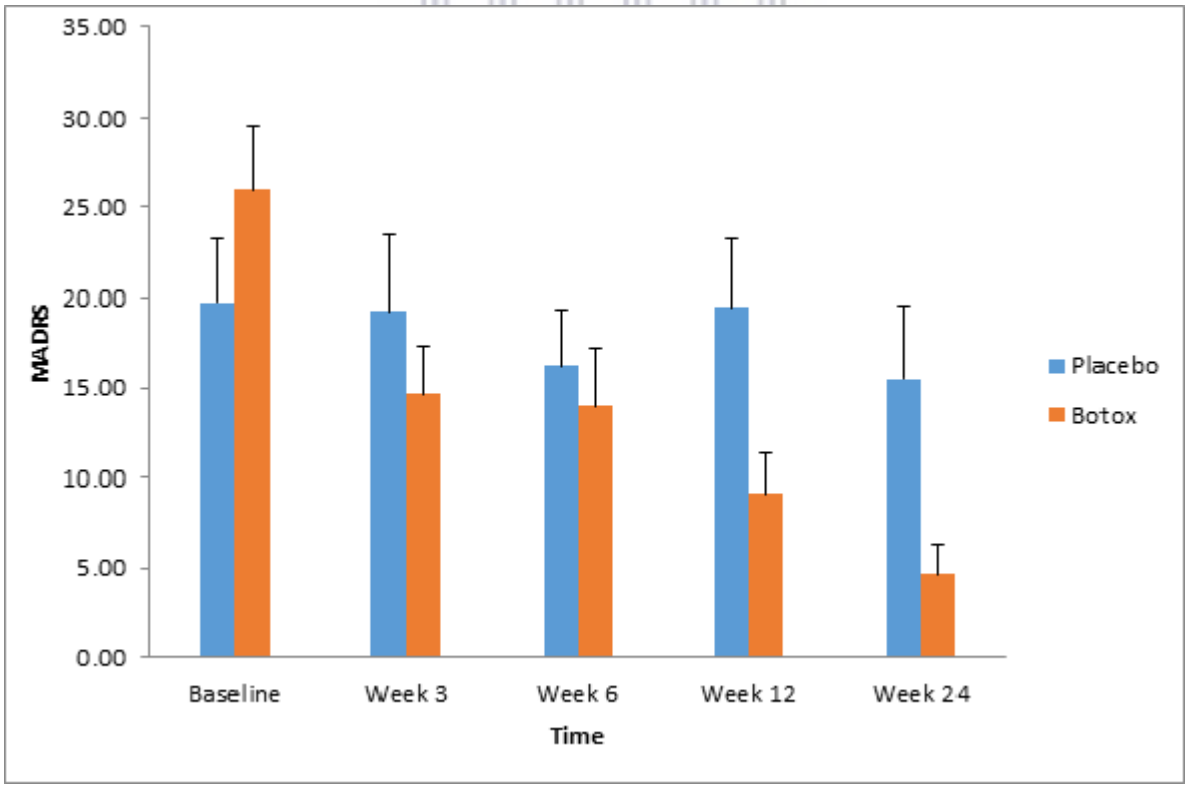

Figure 4. 9: Mean MADRS score of Botox® and placebo group over time

4.5.2 Time Effect of Treatment on Depression as Assessed by the BDI

The results of the Two-way ANOVA for repeated measures showed that there was a significant main effect of the time (weeks) (F (2.5, 44.99) = 9.29, p = 0.000, np^2 = 0.34) on the BDI depression scores overall. From baseline (mean = 25.8, SE = 3.18) the overall BDI depression scores decreased until week 24 (mean = 10.8, SE = 2.13). However, there was no significant main effect between the two groups (F (1,18) = 0.31, p = 0.59, np^2 = 0.02) on BDI depression scores overall.

In dissimilarity, there was a significant interaction between time and the two different groups (F (2.5, 44.99) = 3.10, p= 0.044, np^2= 0.147) in terms of the BDI depression scores. Figure 4.10 shows that for the Botox® group the mean BDI depression scores continued to decrease consistently from the first visit until week 24.

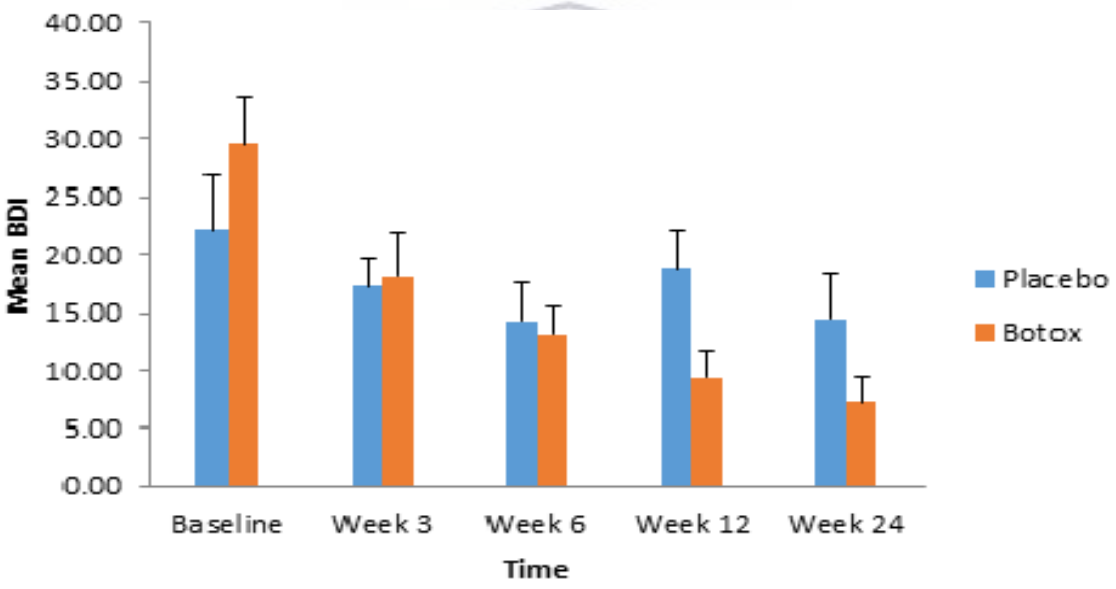

Figure 4. 10: Mean BDI score of Botox® and placebo group over time

4.5.3 Time Effect of Treatment on Quality of Life as Assessed by the QLES-SF

The results of the Two-way ANOVA for repeated measures showed that there was no significant main effect of the time (weeks) ($F(4, 72) = 6.22$, $p = 0.000$, $np^2 = 0.26$) on QLES scores. Additionally, there was no significant main effect between the two treatment groups ($F(1,18) = 0.13$, $p = 0.72$, $np^2 = 0.007$) on QLES quality of life scores overall.

Moreover, there was no statistical significant interaction between time and the two different groups ($F(4, 72) = 1.56$, $p = 0.196$, $np^2 = 0.08$) in terms of QLES quality of life scores. Figure 4.11 shows the mean QLES quality of life scores for the Botox® group continues to increase and is highest at week 12 and week 24.

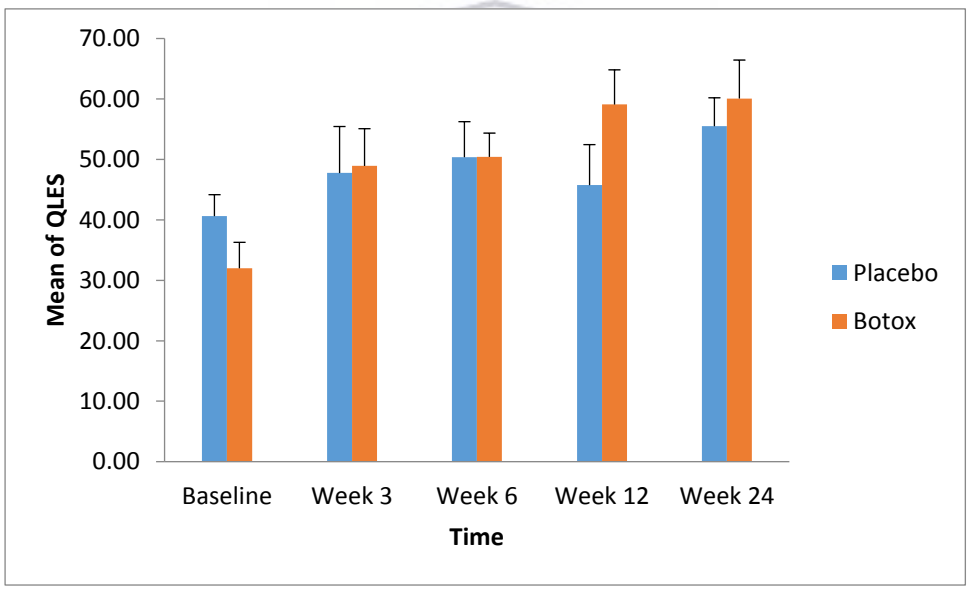

Figure 4.11: Mean quality of life over time

4.5.4 Time Effect of Self-Esteem as Assessed by the RSES

The results of the Two-way ANOVA for repeated measures showed that there was no statistical significant main effect of the time (weeks) ($F(2.5, 44) = 0.57$, $p = 0.21$, $np^2 = 0.08$) on RSES self-esteem scores overall. Figure 4.12 shows the mean RSES scores stayed nearly stable for both the Botox® and placebo group throughout the 24 week period. Also, there was no significant main effect between the two treatment groups ($F(1, 18) = 0.002$, $p = 0.96$, $np^2 = 0.00$) on mean RSES scores overall.

Furthermore, there was no statistical significant interaction between time and the two different groups ($F(2.5, 44.) = 0.57$, $p = 0.96$, $np^2 = 0.000$) in terms of mean RSES scores.

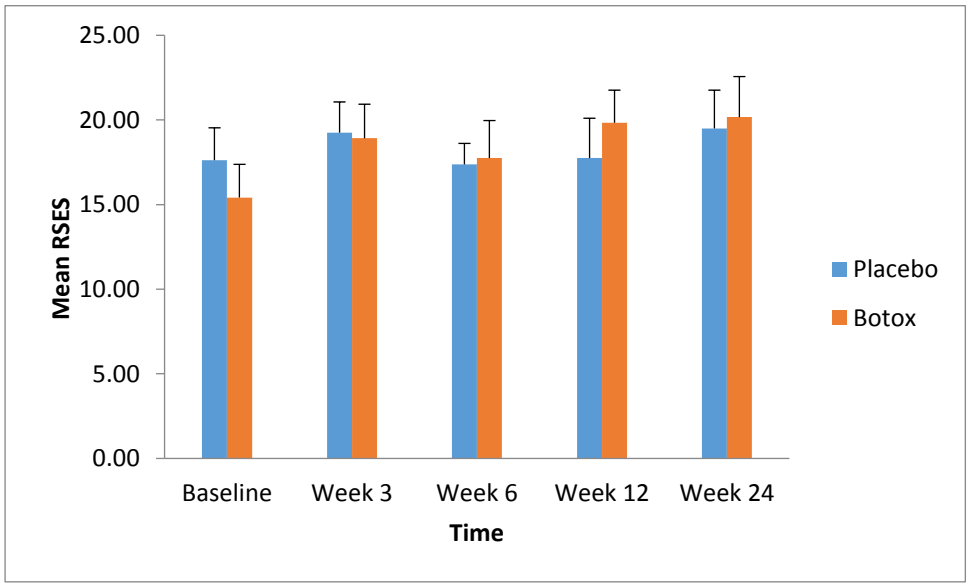

Figure 4.12: Mean RSES over time

4.6 Effect of the MADRS Depression Scores on Self-Esteem

The graph (Figure 4.13) shows, as the mean MADRS depression scores decreases the mean RSES self-esteem increase for the Botox® group. The mean MADRS depression scores and mean RSES for the placebo group is the same at week 3 (MADRS mean = 19.25, RSES mean = 19.25) and week 6 (MADRS mean = 17.25, RSES mean = 17.38).

Figure 4.13: Mean MADRS scores and RSES over time

4.7 Effect of the MADRS Depression Scores on Quality of Life

Figure 4.14 illustrate that as the mean MADRS scores decreases, the mean QLES (quality of life) scores increases throughout the 24 week period for the Botox® group. In the placebo group, the mean MADRS score decreases only slightly at week 6 (MADRS mean = 17.25) and the mean QLES (50.36) score increases. As the mean MADRS (19.13) score increases again at week 12, the mean QLES (45.75) decreases for the placebo group, this pattern continues until week 24.

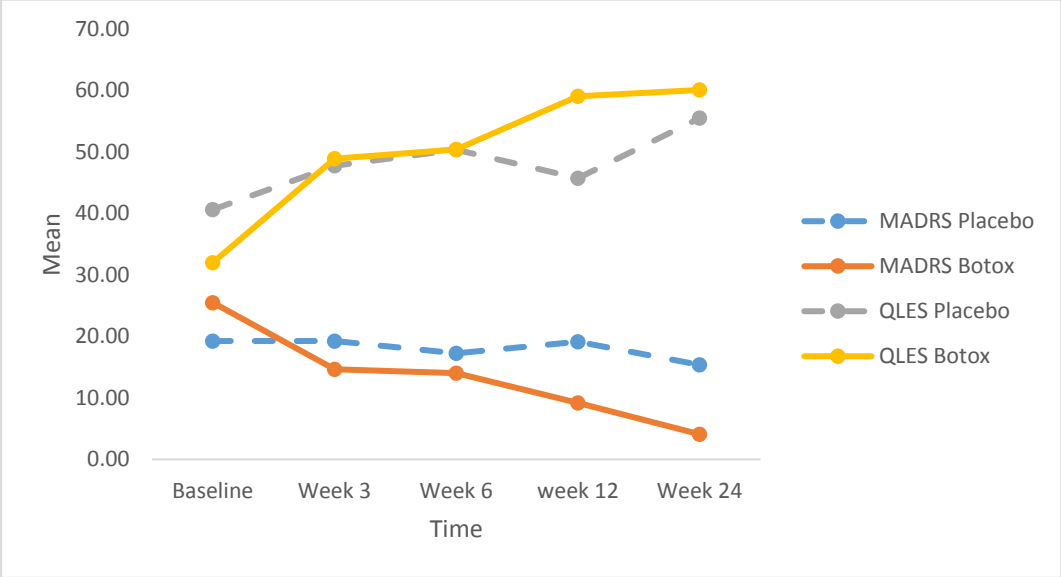

Figure 4.14: Mean MADRS depression scores and mean QLES scores over time

4.8 Effect of the BDI Depression Scores on Self-esteem

Figure 4.15 shows for the Botox® group the mean BDI scores decreasing and the mean RSES almost remaining stable from the first visit throughout the 24 week time period for the Botox® group.

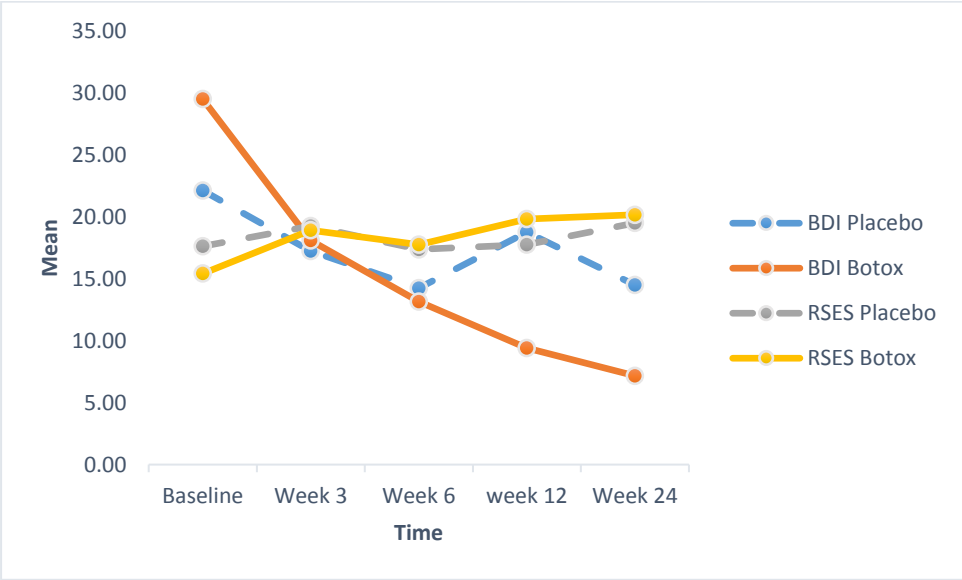

Figure 4.15: Mean BDI and RSES over time

4.9 Effect of the BDI Depression Scores on Quality of Life

As seen in Figure 4.14, as the mean MADRS scores decreases, the mean QLES (quality of life) scores increases from baseline and continues throughout the 24 week time period for the Botox® group. It is notable that a similar trend is observed in figure 4.16 for the Botox group. In the placebo group, the mean BDI score decreases at week 3 (BDI mean = 17.25) and week 6 (BDI mean = 14.25), the mean QLES (47.75) score at week 3 and week 6 (QLES mean =50.37) increases respectively for the placebo group. As the mean BDI (18.75) score increases again at week 12, the mean QLES (45.75) decreases for the placebo group.

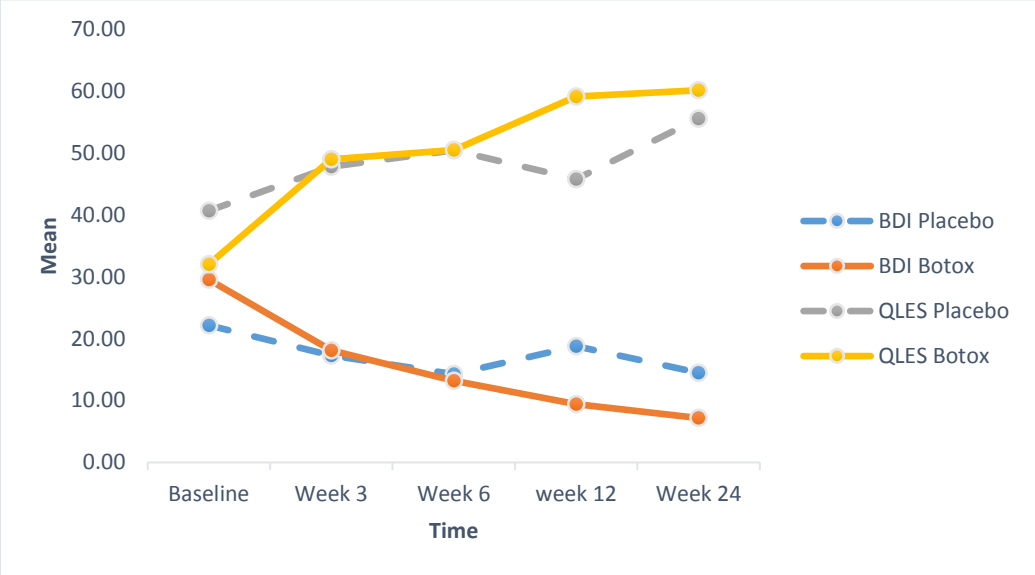

Figure 4.16: Mean BDI and QLES over time

4.10 Self-esteem and Quality of Life

As shown in Figure 4.17, the mean RSES increases for the treatment group, the mean QLES also increases from the visit 1 until the end of the 24 week period.

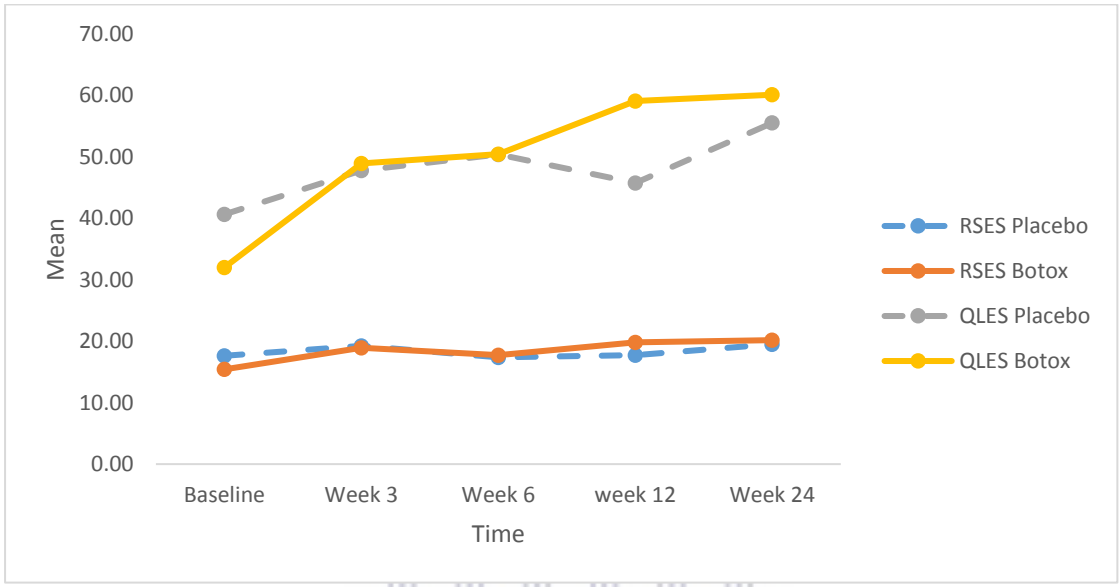

Figure 4.17: Mean RSES and QLES over time

4.11 Chapter Summary

This chapter provides a description of the population sample (demographic profile). Also, it defines the severity of depression of participants at baseline. The chapter also summarizes findings of the secondary and primary outcome measures. It also produces results for the time effect of the Botox® on depression, quality of life and self-esteem. It also produces results for the effect of depression on quality of life and self-esteem. Chapter five discusses the results.

Chapter 5
Discussion

5.1 Introduction

The aim of the study was to explore the effectiveness of Botox® injections for glabellar frown lines as an adjunctive treatment for depression. The effect of Botox® on self-esteem and quality of life of depressed patients was also investigated. The findings of this study are discussed in this chapter.

Studies have shown that the lifetime prevalence rate of major depressive disorder in women (21.3%) is almost double than that in men (12.7%) (Blazer, et al., 1994). Women are known to be more predisposed to depression. There are various biological mechanisms and environmental factors that are implicated in the susceptibility of women to depression. Biological factors include genetic predisposition, hormonal instabilities associated with several aspects of normal reproduction function, and hypersensitivity to such hormonal variations in brain systems that facilitate depressive states (Eriksson, et al., 2002). Psychosocial factors, for example, role-stress, discrimination, gender-specific socialization, and a disadvantaged social-economic status have all been regarded as contributing factors to the heightened predisposition of women to depression (Noble, 2005). The higher female to male participation ratio in the present study was due to only a limited amount of men responding to the advertisements. Men that responded to the advertisement but were not included, did either not meet the inclusion criteria or did not want to undergo Botulinum toxin-A injections, as they had a preconceived idea that Botox® was only for women. Similarly, other antidepressant clinical trials with Botox® also reported a high female to male ratio participation (Wollmer, et al., 2012; Finzi & Rosenthal, 2014; Magid, et al., 2015). The higher female participation can also due to more women suffering from depression (Kessler, et al., 1993).

Depression and cardiovascular disease (CVD) are two of the world's most common health conditions. People suffering from depression have an increased risk of developing cardiovascular disease (Anda, et al., 1993; Ariyo, et al., 2000; Barefoot & Schroll, 1996; Ford, et al., 1998; Penninx, et al., 2001). It has been reported in other studies that patients suffering from depression commonly have concomitant chronic medical illnesses such as hypertension, diabetes, arthritis and cardiovascular diseases (Cassano & Fava, 2002; Cassileth, et al., 1984; Chapman, et al., 2005; Noel, et al., 2004). For instance, depression is linked with changes in health status that may have an impact on the occurrence and progression of heart disease, which includes non-conformance

with medical advice, also the incidence of cardiovascular risk factors, for example, smoking and hypertension. Stress may be an intrinsic factor that triggers the progression of both depression and cardiac disease. The frequency of hypertension was high in this sample population. It was the most prevalent comorbidity. A study conducted by researchers at the University of Witwatersrand showed that South Africa has the highest frequency (between 42% and 54%) of hypertension in Southern Africa, (Gómez-Olivé, et al., 2017). In spite of the growing body of evidence that cardiovascular disease (i.e. Hypertension) and depression are epidemiologically related, the mechanistic relationship between the two is poorly understood.

Unemployed people are said to be in the highest risk groups for major depressive disorder. An association between unemployment and debilitating mental health, particularly depression, has been confirmed in numerous studies (Dooley, Catalano , & Wilson, 1994; Mckee-Ryan, et al., 2005). Long-term or extended unemployment considerably exposes a risk for depression and vice versa: reduced mental health may adversely affect re-employment (Stankunas, et al., 2006; Butterworth, et al., 2012). This could be the reason for the large percentage of unemployed individuals in this sample. The disorder is also linked to loss in productivity in the workplace (Broadhead, et al., 1990). Thus, it places an employee suffering from depression at the risk of losing his/her job. Unemployment may also exacerbate the depression of the affected individual. Due to a poor economic status (financial strain), family life may suffer for example, this may result in marital conflict. Furthermore, unemployment gives rise to financial uncertainty, loss of workplace social relations, time structures and purposeful activity (Paul & Moser, 2009). People with poor mental health find it more challenging in both obtaining and retaining work. Conversely, the argument remains over whether joblessness results in declining mental health or whether those at greater risk of unemployment were in poorer health before becoming jobless (Clausen, Bjorndal, & Hjort, 1993).

Though major depression disorder is manageable, roughly 20% of all people with a major depressive episode acquire a chronic course (Gilmer, et al., 2005; Keller, et al., 1992; Spijker , et al., 2002). The average length of chronic depression is approximately 20 years (Gilmer, et al., 2005). The majority of patients in this study had been living with depression for less than 5 years. Antidepressant medication forms part of the customary care for Depression (Preskorn, Ross, & Stanga, 2004), by which the majority of patients will be given a selective serotonin reuptake inhibitor (SSRI) as first-line drug treatment (Preskorn, Ross, & Stanga, 2004). However, response to first-line pharmacotherapy is usually not optimum (Blier & Mansari, 2013; Connolly & Thase, 2011; Armstrong, 2011). The most common antidepressant used in this study was selective serotonin reuptake inhibitors.

The more frequently or standard criterion used for antidepressant effectiveness in clinical research trials has been a 50% reduction in total HAM-D or MADRS scores from baseline (Prien, Carpenter, & Kupfer, 1991). A more rigorous manner of measuring antidepressant effectiveness is the capacity to bring about remission, this is defined as a clinical state characterised by minimal residual symptoms (e.g. 17-item HAM-D total scores ≤ 7; Frank et al., 1991; MADRS total scores ≤ 10). In the present study, it was observed that repeated treatments (i.e. two treatments) of Botox® in the glabellar region reduces the symptoms of depression. This effect was observed at the third week already and continued until the end of the 24 week follow up period. The study showed a significantly higher reduction in MADRS scores in the treatment group compared to previous studies led by (Wollmer, et al., 2012; Finzi & Rosenthal, 2014). Wollmer, et al., (2012) reported a 41.7% vs 9.2 reduction in HAM-D scores, similarly Finzi & Rosenthal (2014) reported a 47.3% vs 21.1 % reduction in MADRS scores. Whereas, this study observed an 82% vs 21.5% in the Botox® and placebo group and only a 16.4% reduction for the control group in MADRS scores. Thus, this study fully supported the hypothesis that Botox® treatment in the glabellar frown lines reduces depressive symptoms.

Individuals who acquire total remission have a low probability of relapse (Thase, et al., 1992; Fava, et al., 1997) and have more normal psychosocial and occupational functional capacity (Ramana, et al., 1995) in comparison to non-remitted individuals. Remission rates were particularly high for a study with participants suffering from chronic depression. There was already a substantial clinical improvement in patients as of week 3, this was observed by the high remission rate for the Botox® group compared to the placebo group, the remission rate continued to increase considerably until week 24. It was almost twice the rate it was at week 3. The control group had no improvement in their condition. Given the fact that they received no intervention and had no follow up visits, this was an expected outcome. They were only on their current antidepressant medication. This means that their current antidepressant medication did not bring about any clinical improvement in their condition. This further supports the notion that Botox® used together with antidepressant therapy reduces depressive symptoms. However, it cannot be said with 100% certainty that there was not any (albeit small) improvement in their condition throughout the 6 month period, because there might have been an improvement and relapse again prior to the final follow-up visit (week 24). The higher remission rates in this study may be due to the combined effect of the antidepressant medication, Botox® treatment and also the follow up visits. The follow up visits could have had a psychotherapeutic effect. Which may also have contributed to the placebo response. Also due to the fact that they received two treatments of Botox®. The paralytic effect of one dose of Botox® only wears off at about 12-16 weeks (Nigam & Nigam, 2010). Hence, the two repeated treatments of Botox® may have also brought about the sustained and prolonged improvement in the treatment groups' condition. This means that before the effects of the first

treatment of Botox® wore off, patients received another treatment which thus resulted in the continual reduction of MADRS depression scores.

Quality of life measures are being used more and more as an outcome variable in clinical research trials. The aim of measuring quality of life in trials is usually to show or demonstrate how great the impact of a specific mental illness is. Major depressive disorder has substantial effects on quality of life, similarly to other chronic medical conditions, but satisfactory treatment is linked with significant influence on quality of life (Goldney, Phillips, Fisher, & Wilson, 2004). The findings of the present study supported the hypothesis, that Botox® treatment improves the quality of life of depressed individuals. This was demonstrated by the persistent improvement in the mean quality of life of the treatment group. It was observed, as depression symptoms improved, there was a simultaneous/parallel improvement in quality of life. This showed, as patients experienced an improvement in their mood/depressive state (i.e. better mental health), they had a significant improvement in their quality of life. However, the placebo group also displayed an improvement in their quality of life. This could be a result of the follow-up visits-which may have been therapeutic and beneficial to both groups (treatment and placebo group). For the placebo group, it was also illustrated, as their depression increased at week 12, there was a notable drop in their quality of life. This shows, that there was a definite relationship between depression and quality of life. The control group had no improvement in their quality of life. Their quality of life remained constant, thus the same at baseline and at week 24. This further, proves that the follow-up visits had a therapeutic impact. There was a greater increase/improvement in quality of life for the Botox® group than the placebo group. Higher sustained mean quality of life scores was observed at week 12 and at week 24. At week 12, the treatment group received another dose of Botox®. This shows that the aesthetic effect of Botox® also played a significant role in the improvement in quality of life. However, aesthetic effect of Botox® in the glabellar region, cannot by itself be accountable for the marked improvement in quality of life in the treatment group, because there was only a slight improvement in self-esteem.

It was shown in a study by Dayan et al., (2010) that Botox® injection improves self-esteem. However, the results in this study showed, there was only a slight/ small increase in self-esteem. The hypothesis was therefore not supported by the results for the effect of Botox® on self-esteem in this study. This could be because overall patients reported having a normal level of self-esteem at baseline. This is particularly thought provoking as the normal level of self-esteem and high depressive scores at baseline does not support the literature which says depression and self-esteem are closely related. Many studies have supported the view, that depression continually erodes self-esteem over time (Coyne, et al., 1998; Shahar & Davidson, 2003). Thus, the results may not have accurately measured the level of self-esteem in participants due to the small sample size or

participants may have falsely reported a higher self-esteem than the reality. Or it may just be that the current sample had a normal self-esteem.

The term used when individuals display a favourable image of themselves on questionnaires is known as socially desirable responding (SDR). SDR mislead the results of the research by producing false associations or concealing relationships between variables. Socially desirable responding is the tendency for participants to present a favourable image of themselves (Johnson & Fendrich, 2002). The patient may believe the information they present (self-deception), or may be 'faking good' to fit in or follow societal norms or socially acceptable standards, avoid disapproval and obtain social approval, or avoid criticism (King & Bruner, 2000; Huang, Liao, & Chang, 1998). SDR is in all likelihood to arise in responses to socially sensitive questions (King & Bruner, 2000). SDR partiality is also said to considerably affect the validity of questionnaires (Huang, Liao, & Chang, 1998). A measurement tool is termed valid when it correctly and accurately measures what it intends to (Huang, Liao, & Chang, 1998).

How does Botox® improve depression and quality of life? Botox® injected into the glabellar frown muscles, paralyses the muscles temporary. The recipient is therefore unable to produce a frown, which can also be seen as a negative emotion. With the frown muscles paralysed, no negative feedback (facial feedback hypothesis) or impulses can be conveyed to the brain, consequently resulting in a happier mood and improvement in depression symptoms. The paralysis of the corrugator and procerus muscles might lead to a decrease in anger and other negative emotions. Emotions that are unpleasant (i.e. sadness) may still be experienced, but these will not be intensified by equally negative facial expressions (Soussignan, 2002).

Moreover the facial feedback theory postulates that facial expressions largely regulate or balance emotions, rather than being exclusively accountable for it, whatever the facial display these are only a fragment of the complete emotion. Emotions can change or alter, either by reinforcing (intensifying) or weakening the emotional significance of external facial expressions.

The decrease of negative emotions linked with the aesthetic usage of Botox® might also influence a more positive emotional expression. For example, the treatment of Botox® in glabellar muscles (corrugator and procerus muscles) results in the individual not being able to produce a frown hence, the person appears to look happier and less angry this generates or give rise to a more positive emotion and the individual subsequently feels happier. In addition, the happy facial expression, stimulates happier expressions of people the individual interacts with. This further strengthens the positive expression and happy mental state of the affected individual. It has also been proven, when the *Corrugator supercilli* and procerus muscles is paralysed, this causes the person to make use of the other facial muscles more, hence, the person smiles more.

There were too few male participants in the study, thus no conclusion could be made with regards to the effect of Botox® treatment on males. There was also a high participant dropout rate. This could be contributed to the fact that no reimbursement was offered. Many participants in this sample population was unemployed and therefore struggled financially. This resulted in participants having no transport fare to attend follow-up visits. This greatly affected the sample size and subsequently resulted in the small sample size. As patients that did not come for the full duration of the study (all their follow up visits) had to be excluded. Depressed individuals are more predisposed or have a greater tendency to non-compliance. Non-compliance may be an indicator of inadequate health behaviours that are disadvantageous to prognosis; rather, non-compliance may be an indicator of depression (Souery, et al., 1999).

Noteworthy, un-blinding has been a prevailing limitation in many double blind clinical research trials, where numerous researchers have confirmed that at least 75% of subjects correctly guessed which treatment they received at the end of the trial (Bang, Ni, & Davis, 2004; Perlis, et al., 2010). During un-blinding at the completion of this study 75% of patients correctly guessed their treatment. High un-blinding rates are frequently found in antidepressant clinical studies. A study by Perlis et al., (2010) demonstrated that open-label placebo therapy may still bring about a clinical improvement. Participants in this study may have become un-blinded because of the noticeable aesthetic effects of the toxin. The number of follow-up visits may have likely affected the placebo response. Placebo effects has been confirmed to correspond with the number of follow-up visits (Rutherford, Sneed, & Roose, 2009).

This was the first study that measured the effect of Botox® on all four variables simultaneously (i.e. depression, self-esteem and quality of life) as well as the only study that had two treatment doses and three groups, which included a control group which had to limit the placebo response. It was also the first study of its kind in South Africa. In the present study, we show for the first time using a randomized controlled trial design, that repeated treatments (i.e. two doses) of Botox® in the glabellar region reduces the symptoms of depression. It was the second study with Botox® that measured depression over a 24 week period of time.

Conclusion

It can be concluded that repeated treatment of Botox® injections in the *Corrugator supercilli* and procerus muscles result in a sustained improvement in depression and subsequent better quality of life. Botox® used in combination with antidepressants strengthens the antidepressant effect. Furthermore, it supports the facial feedback hypothesis that the facial muscular system emits feedback impulses to the brain. Results of the present study did not indicate any effect of Botox® on self-esteem. The study was limited by the small sample size and high drop-out rate. Future studies should therefore attempt to recruit participants that will be more compliant. It is recommended, that Magnetic Resonance Imaging (MRI's) are taken pre-treatment and post-treatment to visually see the effect of Botox® on the brain more specifically the amygdala. A high frequency of hypertension and depression comorbidity was found in this study. Further studies are thus needed to assess the mechanistic relationship between cardiovascular disease (i.e. hypertension) and depression.

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Appendices

Appendix A: Newspaper Advertisement 1

NEWS

TYGERBURGER Ravensmead & Belhar 3

Glenhaven residents invited to imbizo

All Glenhaven residents are invited to a proposed imbizo by the sector 1 executive and neighbourhood watch which will be held at the Glenhaven Tennis Club on Thursday 23 March.

This will be the first community meeting for the year and important information regarding the current crime stats will be made public by the Bellville South police.

Information regarding crime prevention will include discussion regarding the establishing of street committees, WhatsApp groups and other important matters. There is a request for additional neighbourhood watch patrollers by their chairperson, Rushdien Ryklief, and a report on the positive outcome of their consistent effort.

▸What is your opinion on this article? Let us know at briewe@tygerburger.co.za.

Participants wanted for depression study

A small group of researchers from the department of Medical Biosciences at UWC is looking for volunteers to participate in a study investigating an adjunctive treatment for depression.

The aim of the study is to test the effectiveness of a complementary treatment (treatment combined with a current antidepressant) for depression. Those aged between 18 and 65 years who have been diagnosed with depression and are currently on at least one antidepressant medication, may be eligible to participate in the study.

The research is being conducted at UWC and the duration of the study is six months.

Participants will be required to come for follow-up visits every three weeks.

▸ Anyone interested in participating in this study can call 073 805 0033 or send an email to 3002552@myuwc.ac.za.

Appendix B: Newspaper Advertisement 2

Join study on depression

A small group of researchers from the Department of Medical Biosciences at UWC is looking for volunteers from the Cape Town area to participate in a study investigating an adjunctive treatment for depression.

The aim of the study is to test the effectiveness of a complementary treatment – or treatment combined with current antidepressant – for depression.

If you are aged between 18 and 65 years, have been diagnosed with depression and are currently on at least one antidepressant medication, you may be eligible to participate in the study. The research is being conducted at the university and the duration of the study is six months. Participants will be required to come for follow-up visits every three weeks. According to the World Health Organisation, depression is a major cause of disease burden and disability worldwide, and affects an estimated 350 million people globally. Depression is coupled with functional impairment, high medical cost, and poor quality of life, they state.

A 2015 study carried out by a research company (Hexor), found that 24% of the 1060 South African respondents had been diagnosed with depression, while a study published in 2013 ranked South Africa as the second most stressed country globally. The urgency of this condition requires new interventions/treatments such as those proposed in this study.

▸ Anyone that might be interested in participating in this study, can contact the facilitators on 073 805 0033.

Appendix C: Flyer

Are you suffering from

A group of researchers at the University of the Western Cape is looking for volunteers to participate in an exciting new study investigating an **adjunctive treatment** for Depression.

The **objective** of the study is to investigate the effectiveness of an adjunct treatment for Depression.

About our Study:

- Study will last for a duration of 6 months.
- Subjects will be required to come for follow-up visits every 3 weeks.
- Subjects will receive injectable treatment.
- The study has been ethically approved .

Eligibility:

- Aged between 18-65 years.
- Men and women
- **Diagnosed** with depression.
- Currently on **at least** one antidepressant medication.

Benefits of Study:

- Study treatment
- Follow-up visits with a trained Clinician.
- Over- all better mental health.
- Participation in a groundbreaking innovative study.

If you are interested in participating or need more information.
call: Ms Witbooi @ 0784790513 or
email:3002552@myuwc.ac.za

Appendix D: Information sheet

Project Title: OnabotulinumtoxinA Injection for Glabellar Frown Lines as an Adjunctive Treatment for Depression.

What is this study about?

This is a research project being conducted by Dr Juley De Smidt from the University of the Western Cape in South Africa. We are inviting you to participate in this research project because you meet the set criterion for the population of interest and your participation will help yourself as well as other people.The aim of this research is to investigate the effectiveness of OnabotulinumtoxinA (Botox®) injection for glabellar frown lines as an adjunctive treatment for Major Depressive Disorder. Hence your participation will be of great importance to make this study valuable.

What will I be asked to do if I agree to participate?

You will be asked to sign a consent form agreeing to take part in the study and to receive the study treatment. You will also be asked to fill in 3 questionnaires. You will be asked to come for follow-up visits every 3 weeks for 6 months. The study will be done at the University of the Western Cape focusing on individuals in Cape Town. The follow-up assessments and completing the questionnaires will last approximately 45 minutes at the agreed venue.

Would my participation in this study be kept confidential?

Your personal information will be kept confidential. To help protect your confidentiality, your real names will not be included in the data collection sheets and all information collected will be locked in cabinets and password protected computers. The researcher will use codes to represent your names and only the researcher will have access to such information which will link you to the collected data. During the time when data collected will be reported about this research project, your identity will be protected.

All the data will be kept in password protected computer files known only to the researcher. Data collection sheets and audio tapes will be kept safely in a lockable filling cabinet accessed only by the researcher. All raw data including written documents will be destroyed after three months of the final dissertation being marked and graded. If we write a report or article about this research project, your identity will be protected.

What are the risks of this research?

Risks from participating in this research study mainly include discomfort around providing private or sensitive information. There are no other known risks associated with participating in this research project. If any of the questions asked during the interview make you feel uncomfortable, you are allowed to refrain from answering it.

What are the benefits of this research?

Receiving the study treatment. Having follow-up visits every 3 weeks for 6 months with a trained clinician. The results may help the investigator learn more about BOTOX® treatments and the effects onthe typical symptoms of depression and improves self-esteem. We hope that, in the future, other people might also benefit from this study through improved understanding of the contributions you make in terms of alternative treatment for depression than the conventional antidepressants. This will therefore help to find alternative treatment options for depression and depressive symptoms.

Do I have to be in this research and may I stop participating at any time?

Your participation in this research is completely voluntary. You may choose not to take part at all. If you decide to participate in this research, you may stop participating at any time. If you decide not to participate in this study or if you stop participating at any time, you will not be penalized or lose any benefits to which you otherwise qualify.

Is any assistance available if I am negatively affected by participating in this study?

If at any time of the study, you feel uncomfortable and need assistance, the researcher will refer you for counselling through social welfare office in your area.

What if I have questions?

This research is being conducted by Juley de Smidt, a student pursuing a Doctoral in Medial Biosciences at the University of the Western Cape. If you have any questions about the research study itself, please contact; Juley De Smidt, +27 82 835 1243, jjdesmidt@gmail.com.

Should you have any questions regarding this study and your rights as a research participant or if you wish to report any problems you have experienced related to the study, please contact:

Head of Department: Professor R Henkel

Dept of Medical Bioscience

Dean of the Faculty of Natural Science

University of the Western Cape

Private Bag X17

Bellville 7535

South Africa

This research has been approved by the University of the Western Cape's Senate Research Committee.

Appendix E: Consent Form

Consent Form

Title of Research Project: OnabotulinumtoxinA Injection for Glabellar Frown Lines as an Adjunctive Treatment for Depression

The study has been described to me in language that I understand and I freely and voluntarily agree to participate. My questions about the study have been answered. I understand that my identity will not be disclosed and that I may withdraw from the study without giving a reason at any time and this will not negatively affect me in any way.

Participant's name……..

Participant's signature……

Date……

Should you have any questions regarding this study or wish to report any problems you have experienced related to the study, please contact the study coordinator:

Study Coordinator's Name: Dr Juley De Smidt

Tel: 021 9592182

Email: jdesmidt@uwc.ac.za

University of the Western Cape

Private Bag X17, Belville 7535

Fax: (021)959- 3125

Email: jdesmidt@uwc.ac.za

Appendix F: Demographic Questionnaire

Gender: Female ☐ Male ☐

Age: ☐

1. When were you first diagnosed with depression?
2. How long have you been on antidepressants?
3. What antidepressants are you taking currently?
4. Do you have any other medical conditions?
5. What other medications are you currently using?
6. Are you currently working or unemployed?

Appendix G: Montgomery-Asberg Depression Rating Scale

Montgomery-Åsberg Depression Rating Scale

(MADRS)

Montgomery-Åsberg Depression Rating Scale (MADRS)

1. Apparent sadness Representing despondency, gloom and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.	
0 = No sadness.	☐
2 = Looks dispirited but does brighten up without difficulty.	☐
4 = Appears sad and unhappy most of the time.	☐
6 = Looks miserable all the time. Extremely despondent	☐

2. Reported sadness Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope.	
0 = Occasional sadness in keeping with the circumstances.	☐
2 = Sad or low but brightens up without difficulty.	☐
4 = Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.	☐
6 = Continuous or unvarying sadness, misery or despondency.	☐

3. Inner tension Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.	
0 = Placid. Only fleeting inner tension.	☐
2 = Occasional feelings of edginess and ill-defined discomfort.	☐
4 = Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.	☐
6 = Unrelenting dread or anguish. Overwhelming panic.	☐

4. Reduced sleep Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.	
0 = Sleeps as normal.	☐
2 = Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.	☐
4 = Moderate stiffness and resistance	☐
6 = Sleep reduced or broken by at least 2 hours.	☐

5. Reduced appetite Representing the feeling of a loss of appetite compared with when-well. Rate by loss of desire for food or the need to force oneself to eat.	
0 = Normal or increased appetite.	☐
2 = Slightly reduced appetite.	☐
4 = No appetite. Food is tasteless.	☐
6 = Needs persuasion to eat at all.	☐

6. Concentration difficulties Representing difficulties in collecting one's thoughts mounting to an incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.	
0 = No difficulties in concentrating.	☐
2 = Occasional difficulties in collecting one's thoughts.	☐
4 = Difficulties in concentrating and sustaining thought which reduced ability to read or hold a conversation.	☐
6 = Unable to read or converse without great difficulty.	☐

7. Lassitude Representing difficulty in getting started or slowness in initiating and performing everyday activities.	
0 = Hardly any difficulty in getting started. No sluggishness.	☐
2 = Difficulties in starting activities.	☐
4 = Difficulties in starting simple routine activities which are carried out with effort.	☐
6 = Complete lassitude. Unable to do anything without help.	☐

8. Inability to feel Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.	
0 = Normal interest in the surroundings and in other people.	☐
2 = Reduced ability to enjoy usual interests.	☐
4 = Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.	☐
6 = The experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.	☐

9. Pessimistic thoughts Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.	
0 = No pessimistic thoughts.	☐
2 = Fluctuating ideas of failure, self-reproach or self- depreciation.	☐
4 = Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.	☐
6 = Delusions of ruin, remorse or irredeemable sin. Self- accusations which are absurd and unshakable.	☐

10. Suicidal thoughts Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicide attempts should not in themselves influence the rating.	
0 = Enjoys life or takes it as it comes.	☐
2 = Weary of life. Only fleeting suicidal thoughts.	☐
4 = Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intenstion.	☐
6 = Explicit plans for suicide when there is an opportunity. Active preparations for suicide.	☐

Appendix H: Beck's Depression Inventory

Beck's Depression Inventory

This depression inventory can be self-scored. The scoring scale is at the end of the questionnaire.

1.

2. I do not feel sad.
3. I feel sad
4. I am sad all the time and I can't snap out of it.
5. I am so sad and unhappy that I can't stand it.

2.

0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel the future is hopeless and that things cannot improve.

3.

0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4.

0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5.

0 I don't feel particularly guilty
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6.

0 I don't feel I am being punished.

1 I feel I may be punished.

2 I expect to be punished.

3 I feel I am being punished.

7.

0 I don't feel disappointed in myself.

1 I am disappointed in myself.

2 I am disgusted with myself.

3 I hate myself.

8.

0 I don't feel I am any worse than anybody else.

1 I am critical of myself for my weaknesses or mistakes.

2 I blame myself all the time for my faults.

3 I blame myself for everything bad that happens.

9.

0 I don't have any thoughts of killing myself.

1 I have thoughts of killing myself, but I would not carry them out.

2 I would like to kill myself.

3 I would kill myself if I had the chance.

10.

0 I don't cry any more than usual.

1 I cry more now than I used to.

2 I cry all the time now.

3 I used to be able to cry, but now I can't cry even though I want to.

11.

0 I am no more irritated by things than I ever was.

1 I am slightly more irritated now than usual.

2 I am quite annoyed or irritated a good deal of the time.

3 I feel irritated all the time.

12.

0 I have not lost interest in other people.

1 I am less interested in other people than I used to be.

2 I have lost most of my interest in other people.

3 I have lost all of my interest in other people.

13.

0 I make decisions about as well as I ever could.

1 I put off making decisions more than I used to.

2 I have greater difficulty in making decisions more than I used to.

3 I can't make decisions at all anymore.

14.

0 I don't feel that I look any worse than I used to.

1 I am worried that I am looking old or unattractive.

2 I feel there are permanent changes in my appearance that make me look unattractive

3 I believe that I look ugly.

15.

0 I can work about as well as before.

1 It takes an extra effort to get started at doing something.

2 I have to push myself very hard to do anything.

3 I can't do any work at all.

16.

0 I can sleep as well as usual.

1 I don't sleep as well as I used to.

2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.

3 I wake up several hours earlier than I used to and cannot get back to sleep.

17

0 I don't get more tired than usual.

1 I get tired more easily than I used to.

2 I get tired from doing almost anything.

3 I am too tired to do anything.

4

18.

0 My appetite is no worse than usual.

1 My appetite is not as good as it used to be.

2 My appetite is much worse now.

3 I have no appetite at all anymore.

19.

0 I haven't lost much weight, if any, lately.

1 I have lost more than five pounds.

2 I have lost more than ten pounds.

3 I have lost more than fifteen pounds.

20.

0 I am no more worried about my health than usual.

1 I am worried about physical problems like aches, pains, upset stomach, or constipation.

2 I am very worried about physical problems and it's hard to think of much else.

3 I am so worried about my physical problems that I cannot think of anything else.

21.

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I have almost no interest in sex.

3 I have lost interest in sex completely.

INTERPRETING THE BECK DEPRESSION INVENTORY

Now that you have completed the questionnaire, add up the score for each of the twenty-one questions by counting the number to the right of each question you marked. The highest possible total for the whole test would be sixty-three. This would mean you circled number three on all twenty-one questions. Since the lowest possible score for each question is zero, the lowest possible score for the test would be zero. This would mean you circles zero on each question. You can evaluate your depression according to the Table below.

Total Score_____Levels of Depression

1-10_____These ups and downs are considered normal

11-16_____ Mild mood disturbance

17-20_____Borderline clinical depression

21-30_____Moderate depression

31-40_____Severe depression over 40_____ Extreme depression

Appendix I: Rosenberg Self-Esteem Scale

ROSENBERG SELF-ESTEEM SCALE

The next questions ask about your current feelings about yourself. For each of the following, please circle the number that corresponds with the answer that best describes how strongly you agree or disagree with the statement about yourself now.

		Strongly agree	Somewhat agree	Somewhat disagree	Strongly disagree
1.	I feel that I am a person of worth, or at least on an equal plane with others.	1	2	3	4
2.	I feel that I have a number of good qualities.	1	2	3	4
3.	All in all, I'm inclined to feel that I am a failure.	1	2	3	4
4.	I am able to do things as well as most other people.	1	2	3	4
5.	I feel I do not have much to be proud of.	1	2	3	4
6.	I take a positive attitude toward myself.	1	2	3	4
7.	On the whole, I am satisfied with myself.	1	2	3	4
8.	I certainly feel useless at times.	1	2	3	4
9.	I wish I could have more respect for myself.	1	2	3	4
10.	At times, I think I am no good at all.	1	2	3	4

Appendix J: Quality of Life Enjoyment and Satisfaction

Name:_____ Date:_____

Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)

Taking everything into consideration, during the past week how satisfied have you been with your……

	Very Poor	Poor	Fair	Good	Very Good
…..physical health?	1	2	3	4	5
…..mood?	1	2	3	4	5
…..work?	1	2	3	4	5
…..household activities?	1	2	3	4	5
…..social relationships?	1	2	3	4	5
…..family relationships?	1	2	3	4	5
…..leisure time activities?	1	2	3	4	5
…..ability to function in daily life?	1	2	3	4	5
…..sexual drive, interest and/or performance?*	1	2	3	4	5
…..economic status?	1	2	3	4	5
…..living/housing situation?*	1	2	3	4	5
…..ability to get around physically without feeling dizzy or unsteady or falling?*	1	2	3	4	5
…..your vision in terms of ability to do work or hobbies?*	1	2	3	4	5

…..overall sense of well being?	1	2	3	4	5
…..medication? (If not taking any, check here _____ and leave item blank.)	1	2	3	4	5
…..How would you rate your overall life satisfaction and contentment during the past week?	1	2	3	4	5

Scoring the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)

The scoring of the Q-LES-Q-SF involves summing only the first 14 items to yield a raw total score. The last two items are not included in the total score but are stand-alone items. The raw total score ranges from 14 to 70. The raw total score is transformed into a percentage maximum possible score using the following formula:

$$\frac{\text{(raw total score} - \text{minimum score)}}{\text{(maximum possible raw score} - \text{minimum score)}}$$

The minimum raw score on the Q-LES-Q-SF is 14, and the maximum score is 70. Thus the formula for % maximum can also be written as (raw score −14)/56. The table below converts total raw scores into % maximum scores.

Raw Score	% Maximum	Raw Score	% Maximum	Raw Score	% Maximum	Raw Score	% Maximum
14	0	28	25	42	50	56	75
15	2	29	27	43	52	57	77
16	4	30	29	44	54	58	79
17	5	31	30	45	55	59	80
18	7	32	32	46	57	60	82

19	9	33	34	47	59	61	84
20	11	34	36	48	61	62	86
21	13	35	38	49	63	63	88
22	14	36	39	50	64	64	89
23	16	37	41	51	66	65	91
24	18	38	43	52	68	66	93
25	20	39	45	53	70	67	95
26	21	40	46	54	71	68	96
27	23	41	48	55	73	69	98
						70	100

Citation: Endicott J, Nee J, Harrison W, Blumenthal R. Quality of Life Enjoyment and Satisfaction Questionnaire: A New Measure. Psychopharmacology Bulletin 1993;29:321-326.