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# Patient Reported Efficacy of Botulinum Toxin Type A in the Treatment of Chronic Migraine Headaches

Patrick F. Whitney
*University of South Florida*

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by

Patrick F. Whitney

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Major Professor: Stuart Brooks, M.D.
Thomas Truncale, D.O.
Daisy Chang, Ph.D.

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## ABSTRACT

**Objective:** To assess patient reported efficacy of Botulinum toxin type-A for the prophylaxis of migraine headaches in patients with frequent migraine headaches prior to initiation of treatment with Botulinum toxin type-A compared to post treatment. Questions addressed include is there a difference in frequency of migraine headaches following treatment with Botulinum toxin type-A, is there a difference in cost of conventional treatment versus Botulinum toxin type-A and is there a difference in quality of life.

**Research Plan:** Questions addressed patient status prior to the initiation of treatment as well as post treatment. Patient quality of life change, duration and frequency headache improvement are the primary focus. Other considerations included the cost difference between the previous use of other treatment and the periodic treatment with Botulinum toxin type-A.

**Methodology**: A Cross Sectional study utilizing a questionnaire consisting of a modified Migraine Disability Assessment (MIDAS) questionnaire will be given to patients who had received more than one series of injections. Patients who reported chronic migraine headaches and were refractory to previous treatment methods were screened and placed

in programs utilizing intramuscular injection of Botulinum toxin type-A at standard points on the face, Temporalis muscle and paracervical muscles.

**Clinical Relevance:** This assessment is relevant to occupational issues due to the increasing number of patients applying for disability due to uncontrolled migraine headaches as well as lost productivity and reduction in functional capacity for activities of daily living.

**Impact and Significance:** Patient's that are debilitated by recurrent chronic migraine headaches suffer loss of productive time at work and home. Treatment with Botulinum toxin type-A may results in significant relief allowing fewer days lost at work and improved quality of life. There may be significant cost saving if treatment results in discontinuation of other medications previously used for treatment of migraine headaches.

**Findings:** According to the patients' responses to this survey, it appears that there was an overall improvement in the patients' ability to do work, for those who were employed, as well as their ability to do activities of daily living post treatment with Botulinum toxin-A. Though there were occasionally conflicting data seen in individual cases regarding responses to some of the answers, there appeared to be an overall statistically significant reduction in the mean of responses to the questions. The general implication is consistent with studies that indicate Botulinum toxin-A may be a useful adjunct in the prophylactic treatment of refractory migraine headaches.

## Background

Migraine headaches have become a significant source of lost work in the US. Social Security disability claims arising from migraine headaches have become more increasingly more common in recent years. It is estimated that 30 million Americans suffer occasionally or regularly with migraine headaches. It is estimated that 113 million lost work days are due to migraines with $13 billion of lost productivity (1). Migraine ranks in the top 20 of the world's most disabling medical illnesses. Estimates of the US population suffering from migraine headaches vary in range from 2 - 10% (1,2). The onset of a migraine headache is potentially disabling in itself, however many sufferers live knowing that at any time the onset of a headache could disrupt their ability to work, go to school, care for their families or generally interfere with activities of daily living. Less than 10% of those with migraine history are able to work or function normally during their migraine attacks (1). About 12 million people experience these attacks on an almost daily basis placing them well outside of the average rate of once or twice a month for the typical migraine headache sufferer. These may be referred to as chronic daily headache (CDH) and are defined as a group of disorders characterized by very frequent headaches occurring ≥15 days a month and include those headaches associated with medication overuse (3). In the US, women have a higher prevalence than men at an estimated 18% vs. 6%. Over 30 million people in the United States cause American employers lose more than $13 billion each year as a result of 113 million lost work days due to migraine headaches. In the 2005 European Journal of Neurology, it was estimated that migraine

headaches were the most costly neurological disorder in the European Community costing more than €27 billion per year (15). Annual employer cost of lost productivity due to migraines has been estimated at $3,309 per sufferer. Total medical costs associated with migraines in the United States amounted to one billion dollars in 1994 and when combined with the cost of lost productivity is estimated at thirteen to seventeen billion dollars per year. In a recent aritcle published in the Journal of Occupational and Environmental Medicine, a study was published evaluating the impact on the workplace of chronic migraine headaches as compared to episodic migraine headaches (65). Estimates of lost productivity time were based on 2005 data derived from American Migriane Prevalence and Prevention (AMPP) study. This was a large study surveying 11,000 individuals with migraine headaches. The survey was done on patients over 18 years of age suffering from at least occasional self defined severe headaches. Migraine case definition included established critreia of unilateral or pulsatile pain with nausea, vomiting, phonophobia, photophobia or unusual aura preceeding the headache. The questionairre was initiated in 2004 with a second follow up survey in 2005. The results of the study indicate that individuals with chronic migraine headaches were 19% less likely to be working as compared to those who experienced headaches at less than or equal to 3 headace days per month. The average time lost per week for those with chronic migraine headaches was 4.6 hours as compared to only 1.1 hours per week for those with less frequent headaches. Those in the chronic migraine group accounted for 20.8% of lost productivity time and 35% of overall lost work time when factoring in medical leave and unemployment. The study concluded that the impact of chronic

migraine headaches as well as episodic migraine headaches would be underestimated if employment status is not measured (65).

## Migraine Mechanism

Migraine attacks often include features that occur in sequence beginning with the prodrome stage. This stage is marked by a change in mood that begins hours or days before the headache. Symptoms of prodrome include depression, sleepiness, talkativeness, restlessness, or other alterations (6). Next is the Aura phase characterized by visual abnormalities, including flashes, shimmering, and other hallucinations. Finally the headache phase occurs. The headache itself is typically one sided but may also present as bilateral. It is usually gradual in onset with moderate to severe in pain intensity. Throbbing and worse pain occurs with physical exertion. The headache can last anywhere from 2 hours to 2 days in children and 4 hours to 3 days in adults (6). The frequency of migraine attacks is difficult to predict. The headache stage is often accompanied by decreased appetite, nausea, vomiting, sensitivity to light and sound, blurred vision, tenderness of the scalp or neck, lightheadedness, sweating, and pallor (6). The cause of migraine headaches appears to be multifaceted consequently no single treatment protocol has been uniformly successful leaving migraine patients dissatisfied with treatment results. Numerous theories as to the origin and mechanism of migraine headaches have been proposed over the years. One of the first theories to explain migraines was the classic theory of vasoconstriction/vasodilatation. According to this theory, migraine headaches are caused by the constriction of blood vessels in the brain which is followed by vasodilatation (7). During the 1940s and 1950s, the vascular theory was proposed to explain the pathophysiology of migraine headache. Wolff et al believed

that intracranial vasoconstriction is responsible for the aura of migraine and that the subsequent rebound vasodilatation with activation of perivascular nociceptive nerves resulted in headache. This theory was based on the observations that extracranial vessels become distended and pulsatile during a migraine attack and stimulation of intracranial vessels in an awake person induces headache. He also noted that vasoconstrictors such as ergotamine improve the headache, whereas vasodilators such as nitroglycerin provoke an attack. However, this theory has been challenged recently for several reasons. Brain studies during migraine have shown that blood flow to the brain is in fact abnormal, which likely contributes to the symptoms. The current view is that a complex series of neural and vascular events initiates migraine. This view is now called the neurovascular theory (11). Key features of the neurovascular theory include the following. At baseline, a migraineur who is not having any headache has a state of neuronal hyperexcitability in the cerebral cortex, especially in the occipital cortex (12). This finding has been demonstrated in studies of transcranial magnetic stimulation and with functional MRI. This observation explains the special susceptibility of the migrainous brain to headaches (13). There is speculation that there is a parallel with the patient with epilepsy who similarly has interictal neuronal irritability. The theory of hyperexcitability expands on the theory of vasoconstriction/vasodilatation. According to the theory of hyperexcitability, the brains of migraine sufferers are more sensitive to normal triggers, such as stress. The frequency of migraines depends on the level of excitability. An external trigger may stimulate sudden constriction of the blood vessels in the brain resulting in the onset of a migraine headache. It is theorized that the cause of this excitability is due to abnormal brain chemistry, specifically in the relationship between

calcium and magnesium. Calcium flows from the extracellular fluid to the intracellular space during periods of nerve excitability resulting in vasoconstriction. In theory anything that blocks the flow of calcium or restores the balance of magnesium to calcium would be helpful in mitigating migraine. Some studies have shown that calcium channel blockers can successfully prevent migraine attacks due to blocking the flow of calcium into cells (8). Another theory proposes that there is a derangement of serotonin metabolism and an excess of neurotransmitters. During migraine, serotonin levels are depressed in the brain. Triptans selectively stimulate certain serotonin receptors and have been shown to reduce the symptoms of migraine (9). This theory is supported by the fact that melatonin, secreted by the pineal gland along with serotonin, is also reduced during migraine. This suggests that the pineal gland is depressed in migraine patients (10). High levels of steroid hormones, primarily estrogen, can interact with the serotonin transport system. This further compromises the availability of serotonin. Other parts of the nervous system are also implicated in migraines. The sympathetic nervous system is responsible for many functions including increasing the contractility of smooth muscle and increasing the heart rate. Many of the reported factors that trigger migraine, such as stress and hormonal changes, also act on the sympathetic nervous system (9). Similarly, drugs that mimic or enhance norepinephrine may alleviate migraine (9). Some evidence implicates steroid hormonal imbalances in migraine. Reports by women note that their migraine attacks occur in connection with their menses. Abnormal hormone levels have been suspected as closely associated with migraine headaches. As previously discussed, occasionally a small percentage of migraine sufferers will fall into the category of chronic daily headaches. Current diagnostic criteria used to define CDH were published

by the International Headache Society in 2004. According to these criteria, primary chronic daily headache (CDH) is defined as daily or almost daily migrainous headache that occurs for more than 15 days a month, for greater than 3 months, and has no structural or infectious causes. Associated symptoms of nausea, vomiting, photophobia, and phonophobia may be less frequent in chronic migraineur. The pathogenesis of chronic daily headache is not well understood, and some believe that it is due to a central mechanism involving an alteration in serotonergic and monoaminergic pathways to the brainstem and hypothalamus (14). Chronic daily headaches have been associated with an increased frequency of primarily psychiatric comorbid conditions such as depression, anxiety, bipolar disorders, panic attacks, oromandibular dysfunction, stress, and drug overuse.

## Management

Acute treatment of migraine headaches involves the use of medications intended to relieve the symptoms of attacks when they occur. Migraine headache preventative efforts involve the use medications taken daily to reduce the number of attacks and lessen the intensity of pain. Some patients may respond to alternative treatment such as lifestyle changes, relaxation techniques, acupuncture, exercise, proper rest and dietary modification. Typically these are referred to as complementary treatment and may help avoid the triggering of attacks. Medication overuse, commonly known as rebound headache, can have a significant influence on initiation of migraine headaches (4). Standard medical approach to managing migraine headaches include preventative or prophylactic measures, trigger management, abortive measures and pain management of the headache once it occurs. Typically preventative measures have relied on the use of medications that were never intended to treat headaches. These include beta blockers, calcium channel blockers, Methylsergide or Divalproex Sodium. Beta-blockers, primarily Propranolol, are one of the most commonly prescribed prophylactic treatments for Migraine and are considered to be an effective preventive treatment. Calcium channel blockers are thought to play a role in migraine prevention by affecting blood vessel constriction as previously discussed. Methysergide is thought to block the inflammatory and vessel-constricting effects of serotonin. Because of potential side-effects, Methysergide is generally used only on select patients. Some of the known potential side effects include retroperitoneal fibrosis which may be severe but

uncommon. Other severe but uncommon side effects include pleural fibrosis and subendocardial fibrosis as well as an increased risk of left-sided cardiac valve dysfunction (5). Because of the potential severity of these side effects, Methysergide requires a four to six week drug hiatus every six months. Divalproex Sodium was originally developed for Epilepsy. It is typically prescribed in smaller doses to treat migraine headaches to reduce the potential side effects. Management of migraine triggers are effective if the trigger is known and can reasonably be avoided. Triggers are different from person to person. Some examples of reported triggers include changes in weather or air-pressure, bright sunlight, glare, fluorescent lights, chemical fumes, menstrual cycles, and certain foods such as processed meats, red wine, beer, dried fish, broad beans, fermented cheeses, aspartame, and MSG. Once the prodromal phase of the migraine occurs and the headache is imminent, abortive measures may be initiated. Abortive medications are used to relieve the severity, duration and associated symptoms of the migraine headache. They are recommended to taken as early as possible in an attack. Cerebral vasoconstrictor abortive agents were formulated specifically for migraine headaches. They may be administered by subcutaneous, oral, rectal, or intramuscular means. Some of the common medications include ergotamine tartrate or Dihydroergotamine, Sumatriptan, Naratriptan, Rizatriptan, Zolmitripan, Electriptan, Frovatriptan and Isometheptene mucate. The nonvasoconstrictive abortive agent Butorphanol tartrate may be administered by injection or nasal spray. Emergency departments commonly use narcotic injections in combination with Promenthazine or Hydroxyzine for nausea. These can offer an option if other measures fail or are not appropriate for comorbid conditions such as heart disease or other medical condition that

would contraindicate their use. Once the headache starts, pain management may include narcotic analgesics. These act on the nervous system receptors and alter the patient's perception of pain. These drugs may relieve pain, however they may be addictive and such usage should be done in an appropriate manner. Common narcotic medications include Butalbital with Codeine, Codeine, Acetaminophen and Oxycodone hydrochloride, Meperidine hydrochloride, acetaminophen and codeine, Hydrocodone bitartrate and acetaminophen or methadone. Though normally ineffective for relief of migraine headaches, NSAIDs (non-steroidal anti-inflammatory drugs) act by inhibiting blood vessel inflammation. These medications include Naproxen, Ibuprofen and Ketorolac. Most are readily available over the counter in non prescription doses which makes them accessible to the general public. Many migraine headache sufferers take these OTC medications in inappropriate doses in a desperate attempt to relieve a debilitating painful condition. Some migraineurs attempt to manage mild to moderate attacks at home by using a variety of techniques which include using a cold compress to the area of pain, resting with pillows comfortably supporting the head or neck in a room with little or no sensory stimulation (light, sound, odors), avoiding stressful surroundings, sleeping or consuming a moderate amount of caffeine. Other alternative treatments include but are not limited to acupuncture, biofeedback, manipulation, massage and nutritional (herbs, vitamins, minerals). Lifestyle and home remedies, as described by the Mayo Clinic staff on their web page regarding migraines, mayoclinic.com, can include muscle relaxation exercises, proper rest and keeping a headache diary to help learn more about what triggers the migraines and what treatment is most effective. They also indicate that Botulinum toxin type A is sometimes used for treatment of chronic

migraines. They state that studies have had mixed results with respect to effectiveness but that some headache specialists believe that it can be helpful for some people. Injections are made in muscles of the forehead and neck. When this is effective, the treatment typically needs to be repeated every three months.

## Botulinum Neurotoxin Overview

Botulinum toxin is a neurotoxic protein produced by the bacterium Clostridium botulinum, and is held to be the most toxic substance known to mankind (16) with an LD50 of roughly 0.005–0.05 µg/kg. The flaccid muscular paralysis can be fatal in cases of botulism. Ironically, this property is intentionally used as an advantage in medical treatments. The toxins are injected into the muscles at different sites on the body resulting in temporary paralysis with effects lasting from 3 to 9 months. The toxin is a microbial product synthesized by the anaerobic, gram-positive, spore forming bacteria ubiquitously found in the soil. Historically Botulinum toxin has been considered a byproduct of the bacteria resulting in spoiled food. The Botulinum toxin's most significant adverse health effect is its prevention of neurotransmission causing paralysis. Death occurs from Botulism primarily as a result of paralysis of the respiratory muscles leading to respiratory failure (19). German physician Justinus Kerner (1786-1862) first developed the idea of a possible therapeutic use of Botulinum toxin which he called "sausage poison". In 1928, Dr. Herman Sommer, at the University of California, San Francisco, first isolated in purified form Botulinum toxin type A (BoNT-A) as a stable acid precipitate. In the 1950s, Dr. Vernon Brooks discovered that when BoNT-A is injected into a hyperactive muscle, it blocks the release of acetylcholine from motor nerve endings. Work with Botulinum toxin type A as a therapeutic agent to treat human disease began in the late 1960s through the collaboration of Alan B. Scott, MD, of the Smith-Kettlewell Eye Research Foundation and Edward J. Schantz, PhD, director of food

microbiology and toxicology at the University of Wisconsin. This is when Botulinum toxin type A was first considered as a powerful therapeutic agent to treat symptoms of neurological disorders rather than an agent of human sickness and disease. In 1980, Dr. Alan B. Scott, of Smith-Kettlewell Eye Research Institute, used Botulinum neurotoxin-A for the first time in humans to treat strabismus. In December 1989, BTX-A (BOTOX) was approved by the FDA for the treatment of strabismus, blepharospasm, and hemifacial spasm in patients over 12 years old. Although the effect had been observed by a number of independent groups, the cosmetic effect of BoNT-A was initially described by ophthalmologist Jean Carruthers and dermatologist Alastair Carruthers working in Vancouver, Canada. The FDA announced the approval of BOTOX® Cosmetic on April 15, 2002 as a treatment to temporarily improve the appearance of moderate to severe frown lines between the eyebrows referred to as glabellar lines. BoNT is broken into 7 neurotoxins labeled types A, B, C [C1, C2], D, E, F, and G. They are all antigenically and serologically distinct but structurally similar. Human botulism is primarily caused by types A, B, E, and F. Types C and D are only toxic in animals. The toxin is a zinc dependent protease that cleaves one or more of the fusion proteins by which neuronal vesicles release acetylcholine (Ach) into the neuromuscular junction. It acts preferentially on peripheral cholinergic nerve endings to block Ach release (18). The details of BoNT mechanism are described by Takamizawa K, Iwamori M and Kozaki S, et al. The BoNT molecule is synthesized as a single chain and then cleaved to form the dichain molecule with a disulfide bridge. The light chain acts as a zinc endopeptidase similar to tetanus toxin with proteolytic activity located at the N-terminal end. The heavy chain provides cholinergic specificity and is responsible for binding the toxin to presynaptic receptors. It

also promotes light chain translocation across the endosomal membrane. Botulinum toxin acts by binding presynaptically to high affinity recognition sites on the cholinergic nerve terminals. This results in decreased the release of acetylcholine causing a neuromuscular blocking effect. Specifically, Botulinum toxin cleaves SNARE proteins which are involved with fusing synaptic vesicles to the plasma membrane. Cleaving of SNARE proteins inhibits the release of acetylcholine at the neuromuscular junction leading to inhibition of neurotransmission. Cleaving SNARE proteins creates a nonfunctional SNARE complex disrupting calcium influx and fusion is disrupted. Increasing the calcium concentration in the synaptic terminal may diminish the effects of Botulinum toxin. According to de Paiva A, Meunier FA, Molgó J, et al, recovery occurs through proximal axonal sprouting and muscle reinnervation by formation of a new neuromuscular junction. BoNT-A and BoNT-E cleave synaptosome associated protein (SNAP-25), a presynaptic membrane protein required for fusion of neurotransmitter-containing vesicles (17). When BoNT-A is injected into a striate muscle, paresis occurs after two to five days and lasts from two to three months before it gradually starts to wear off. When Botulinum Toxin is injected into a target tissue it is almost completely bound to the axon terminal (20). However, when BoNT-A is applied to treat cervical dystonia, small fractions of the applied Botulinum toxin are distributed systemically and can be detected by increase of neuromuscular jitter in non injected muscles (21). When Botulinum Toxin-B is applied to treat cervical dystonia substantial systemic anticholinergic side effects can be clinically detected (18). Despite its systemic distribution, direct Botulinum Toxin effects on the CNS have not been reported. This is because Botulinum neurotoxin with its size of 150 KiloDalton does not penetrate the blood brain barrier. Apart from

systemic penetration Botulinum toxin could theoretically reach the CNS by retrograde axonal transport. Such retrograde axonal transport has been detected for Botulinum toxin with radioactively labeled Botulinum neurotoxin (22). The Botulinum toxin was likely inactivated before it reached the CNS since the retrograde axonal transport was so slow. Transsynaptic transport was not observed. Botulinum Toxin action upon Renshaw cells was only demonstrated after intraspinal injection (23). Effects of Botulinum Toxin on the neuromuscular synapse and on the muscle spindle organs can produce various indirect effects on the CNS. On the spinal level Botulinum Toxin produces reflex inhibition of alpha motoneurons by gamma motoneuron blockade and subsequent Ia/II afferent input suppression1(24,25). Botulinum toxin may normalize altered reciprocal inhibition between flexor and extensor muscles in patients with upper limb dystonia (26). A similar effect was also demonstrated in patients with essential tremor (27). EMG changes of the contralateral ocular muscles after injection of Botulinum toxin into the lateral rectus muscle also suggest central effects (28). Botulinum toxin may also normalize altered intracortical inhibition at the supraspinal level (29) as well as altered somatosensory evoked potentials (30). Although Botulinum toxin can enhance some aspects of cortical activation it fails to improve the impaired activation of the primary motor cortex as seen in writer's cramp (31). When Botulinum Toxin is used to treat painful muscle hyperactivity disorders frequently substantial pain relief is reported. Pain relief is usually attributed to the reduction of the muscle hyperactivity. However, formalin-induced pain in animals can be reduced by Botulinum toxin direct analgesic effect (32). Substance-P is a neuropeptide involved in pain perception, vasodilatation and neurogenic inflammation. It has been shown to be blocked by Botulinum toxin together with acetylcholine in the

iris muscles of rabbits (33) as well as in cultured dorsal root ganglia neurons (34). Direct Botulinum toxin effect is suggested due to this association of inhibition with a decrease of SNAP 25. Botulinum Toxin induced suppression of substance-P has also be demonstrated in embryonic rat dorsal root ganglia neurons (35). When different Botulinum toxin serotypes were tested, Botulinum Toxin-A produced the strongest substance-P suppression (35). Botulinum Toxin has also been shown to suppress the release of glutamate, another neurotransmitter involved in nociception, in the periphery and in the dorsal horn (36). This confirmed earlier findings of Botulinum toxin induced inhibition of glutamate release from cerebrocortical synaptosomes (37). The release of noradrenalin in PC12 cells (38), used as a model system for neuronal differentiation, and calcitonin gene related peptide in autonomic vascular nerve terminals (39) could also be reduced by Botulinum Toxin suggesting additional possible mechanisms for Botulinum Toxin effects on pain transmission (40).

## Clinical uses for Botulinum Neurotoxin

According to the FDA website, www.fda.gov, information regarding approved preparations of Botulinum toxin products is limited to 3 preparations of Botulinum neurotoxin type A. They are marketed by 2 companies under the labels Botox, Botox Cosmetic and Dysport. The only listed indications for use according to the FDA site are for cervical dystonia, severe primary axillary hyperhidrosis, strabismus, blepharospasm, and temporary improvement in the appearance of moderate to severe glabellar lines. Considerations for health care professionals section states that a boxed warning has been added to the prescribing information to highlight that Botulinum toxin may spread from the area of injection to produce symptoms consistent with botulism. Symptoms such as unexpected loss of strength or muscle weakness, hoarseness or dysphonia, dysarthria, loss of bladder control, trouble breathing, trouble swallowing, double vision, blurred vision and drooping eyelids may occur. Swallowing and breathing difficulties can be life threatening and there have been reports of deaths related to the effects of spread of Botulinum toxin. It also states that clinical doses expressed in units are not comparable from one Botulinum toxin product to the next. Units of one product cannot be converted into units of another product thus Botulinum toxin products differ from one another in dose units, names, and dosing and are not interchangeable. In November 2001, Health Canada approved Botox injections to reduce spasticity that can occur after a stroke. Allison Brashear, MD, professor and chair of the Neurology department at Wake Forest University Baptist Medical Center in Winston Salem, N. C., directed the first major study

in 2002 on the use of Botox for post stroke muscle spasticity (41). The results were published in the New England Journal of Medicine. In that multi-center study, half of the 126 patients received Botox and the other half took a placebo. 62% of the Botox group reported improvement in the area they desired as opposed to just 27% of the placebo group. In that study, patients received just one injection. In 2005 at the annual meeting of the American Association of Physical Medicine in Philadelphia, Dr. Brashear presented the findings of the first long-term study of the repeated use of Botulinum toxin type-A for the treatment of post stroke spasticity. The study focused on 279 patients at 35 rehabilitation centers in Indiana over a 1 year period. The research was funded by the company that manufactures Botox, Allergen Inc. The participants in the study had hand, wrist or elbow spasticity. Up to five doses were given to targeted muscles in the wrist, elbows and fingers. Six weeks into the study researchers discovered a notable improvement in patients' muscle tone from the onset of treatment. Improvement was graded in four areas consisting of pain, hygiene, dressing and limb posture. At least half the participants by the end of the study reported that they had improved by one point in the area they deemed most significant. Despite these results, treatment for muscle spasticity remains an off label use. Several other off label uses of Botulinum toxin-A has been and are currently used in practices of various subspecialties. Some of the more common off label uses include low back pain, dystonia, laryngeal spasm, hemifacial spasm and migraine headaches. Since the nature of this study involves treatment using Botulinum toxin-A for migraine headaches, I will focus on information to that use.

## Supportive Studies

Chronic daily headaches (CDH) are a heterogeneous group of headache disorders occurring on at least 15 days per month that, according to population studies, affects 4% to 5% of the general population worldwide (42-45). Chronic migraine is in the subset of the CDH disorders. Chronic migraine was first characterized by Silberstein and Lipton. By definition it includes head pain occurring on 15 or more days per month, headache duration of 4 or more hours and increasing headache frequency with decreasing symptom severity over a 3-month period (46-47). The two most common forms of primary, long duration CDH disorders are chronic (transformed) migraine and chronic tension headaches, with most subclassified as transformed migraine (48-50). While most CDH patients are categorized as having transformed migraine others may have chronic tension type headache (51-52). Transformed migraine may also be associated with medication overuse headache (53,54). As indicated previously, the current standard treatment for migraine headaches includes primarily medications designed to abort an imminent headache or manage the pain associated with the headache once it starts. Chronic migraine is often both common and resistant to treatment even with prophylactic medications known to be effective in patients with episodic migraine headaches (55). Medications used to treat chronic migraines include simple analgesics as well as prophylactic medications that were originally designed to treat other conditions such as depression, hypertension, and seizures. Practitioners often struggle with decisions on how to best manage patients who present with persistent migraine headaches that have

shown little lasting response to standard medication regimens and are either utilizing excessive amounts of prescription medications or showing poor response to medications prescribed with no other explanation as to why their headaches persist. The disability and impact associated with this disorder is substantial and touches almost every aspect of the patient's life. These patients experience significantly diminished health-related quality of life. Mental health as well as physical, social, and occupational functioning may also be impaired (56). Many alternative methods of management as previously listed also have had mixed results. Interest in the use of botulinum toxin-A was first generated following an observation by practitioners using the commercial preparation for cosmetic purposes following the initial approval by the FDA. When doing procedures involving injections to remove glabellar lines, patients who had previously experienced frequent migraine headaches reported a reduction in the frequency and intensity of headaches. Since 1992, Botulinum toxin-A had been used in purified and diluted form to temporarily paralyze the Corrugator and Procerus muscles that bring the eye brows together to eliminate wrinkles in this region. The practice of injecting the area with Botulinum toxin-A in the upper third of the face for treatment of cosmetic frown lines in patients who coincidentally suffered from Migraines, resulted in the reported unexpected benifit of migraine relief (57). During the November 2-5, 2000 American Society of Dermatologic Surgery meeting , Richard Glogau, MD, University Of California, San Francisco professor of dermatology presented a study that he performed at UCSF. He reported that 75 % of patients in his case study experienced four to six months of Migraine relief following injections of Botulinum toxin-A into muscles of the face and head. Glogau's small study of 24 patients added weight to previous reports that Botulinum toxin-A can relieve Migraines.

Following this opportune discovery, Dr. Glogau and other researchers began to evaluate injection points and dosages that could alleviate Migraines. Dr. Glogau's results indicated that Botulinum toxin-A injected into the muscles of the brow, eyes, forehead, side of the head and back of the head near the neck provoked sometimes immediate migraine relief and provided benefit for up to six months. The dosage of Botulinum toxin-A in his case studies averaged 80 units per patient (57). Unfortunately most of the data at that time consisted of case reports and meeting abstracts. There were no published randomized double-blind trials that demonstrated safety and efficacy of Botulinum toxin-A for treatment of migraines. There were only two previous studies which were presented at the 1999 meeting of the American Association for the Study of Headache (currently the American Headache Society). The first study was reported by researchers at the Michigan Head Pain and Neurological Institute in Ann Arbor and Michigan State University. The study involved a procedure using a one time dose of 25 units of Botulinum toxin A injected into the muscles of the brow, forehead and side of the head. The results of this study reflected a reduction in the frequency of Migraines, the severity of pain, vomiting, and the use of pain medications for up to three months. Treatment with 75-units resulted in migraine relief but also elicited undesirable side effects like eyelid drooping. In the second study, reported by researchers at the University of California, Los Angeles, 51% of 96 patients reported complete improvement of their Migraine pain (57). Other researchers developed an interest and proceeded to set up their own studies following these reports of migraine relief using Botulinum toxin-A. In 2004, Stafford Conway, M.D. et al, undertook an open label study to evaluate the safety and utility of Botulinum toxin type-A injection therapy for patients with chronic migraine who

previously had failed to respond to at least three prophylactic medications. The study at the University of South Alabama Headache Center in Mobile, Al. involved a total of 59 patients. An inclusion criterion was that the patient had previously failed at least three adequate trials of prophylactic medications known to be effective in treating episodic migraine. All participating patients were asked to complete a Migraine Disability Assessment (MIDAS) questionnaire and to keep a headache diary for the month preceding Botulinum toxin type-A administration. All patients received 25 units of Botulinum toxin type-A per the fixed frontal-temporal site protocol published by Silberstein et al (58). Participating patients were asked to return for follow-up 6 weeks after Botulinum toxin type-A treatment and present their headache diary including any perceived side effects. Their report included only a descriptive analysis of the results. A "positive response" was defined to be a 50% or greater reduction in headache days per month over the last 30 days of the follow-up period relative to the patient's baseline status. Other outcome variables analyzed included subjective response ("much better," "somewhat better," "same," or "worse") and functionally incapacitating headache days per month over the last 30 days of the follow-up period relative to the 30 days pretreatment. Their results showed a 41% positive response rate however their conclusion stated that "Based on our observations and results from other published reports, we offer for speculation the possibility that the current uncertainty regarding the efficacy of BoNT-A for prevention or suppression of migraine may reflect a type II error; that is, even the large-scale studies performed to date have involved too few patients overall and included too many subjects predestined to fail." One of the most frequently referenced studies was a multicenter trial funded by Allergan Inc., the makers of Botox

(BoNT-A ) which was used in the study. This was one of the first randomized, double-blind, placebo-controlled study of Botulinum toxin type-A in patients with diagnostic criteria of CDH and was conducted from July 6, 2001, through November 7, 2003, at 28 North American study centers. The study was headed by Stephen D. Silberstein, M.D. in cooperation with the Bonta-039 Study Group. The study was a randomized, double-blind, placebo-controlled, parallel group clinical study of 3 fixed-dose treatments of Botulinum toxin type-A compared with placebo in the treatment of patients with CDH. Inclusion criteria for the study included men and women aged 18 to 65 years who experienced headaches on more than 15 days during a 30-day baseline screening period. Headaches could include any combination of migraines with or without aura, migrainous headache, probable migraine, and/or episodic or chronic tension-type headaches. Included were long-term prophylactic headache medications however they had to be stable with no change in dose or dosing regimen for at least 3 months immediately before the baseline period. Patients were excluded from the study if they had any medical condition such as neuromuscular disorders or used any agent that might expose them to risk if they received Botulinum toxin type-A, had an infection or skin problem at any of the injection sites, had a known allergy or sensitivity to the study medication or to its components as well as other exclusions listed in the study (60). This was a double-blind study and neither the investigator nor the patient knew which treatment was given at day 0, day 90, and day 180. Among 1200 screened patients, 702 (mean age 43.4 years with 82.9% female) were enrolled, entered into the placebo run-in period, and subsequently randomized to active treatment or placebo at day 0. At the end of the placebo run-in period, of 702 patients, 538 were classified as placebo nonresponders and 164 as placebo

responders. Subsequently, patients within each group were randomized to receive Botulinum toxin type-A at 225 U (n=182), 150 U (n=168), 75 U (n=174), or placebo (n=178). The primary efficacy end point was the mean change from baseline in the frequency of headache-free days for the 30-day period ending on day 180 for the placebo nonresponder group. A secondary efficacy end point was the proportion of patients with a decrease from baseline of 50% or more in the frequency of headache days per 30-day period at day 180 for the placebo nonresponder group. Other variables evaluated per 30-day period included the frequency of any type of headaches, the proportion of patients with a decrease from baseline of 50% or more headaches, the frequency of migraine headaches of any severity, the proportion of patients with a decrease from baseline of 50% or more in migraine headaches, the proportion of patients with a decrease from baseline of 2 or more migraine headaches, and the frequency of moderate to severe migraine headaches. Although the primary efficacy end point was not met, Botulinum toxin type-A treatment in this trial showed a significant difference from placebo in some analyses. At day 240, the decrease in headache frequency was significantly greater for the Botulinum toxin type-A 225 U and 150 U groups compared with placebo. The placebo response was higher than expected but a greater percentage of patients in the placebo group used pain medications for acute headache throughout the study, thereby confounding the results (60). A later study was published in Headache April 2005 by Mathew NT, Frishberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C; BOTOX CDH Study Group. This was an 11-month, randomized double-blind, placebo-controlled study of Botulinum toxin type-A for the treatment of patients aged 18 to 65 years old with 16 or more headache days per 30 days conducted at 13 North American study centers. The

primary efficacy measure was the change from baseline in the frequency of headache-free days in a 30-day period for the placebo nonresponder group at day 180, the chosen efficacy time point. The secondary efficacy measure was the proportion of patients with a decrease from baseline of 50% or more in the frequency of headache days per 30-day period for the placebo nonresponder group at day 180. The change from baseline in the frequency of headaches per 30-day period, the proportion of patients with a decrease from baseline of 50% or greater in the frequency of headaches per 30-day period, acute medication use, and adverse events were also assessed. 355 patients, with a mean age of 43.5 years and 84.5% female, were enrolled and randomized (59). At day 180, placebo nonresponders treated with Botulinum toxin type-A had an improved mean change from baseline of 6.7 headache-free days per 30 day period compared to a mean change from baseline of 5.2 headache-free days for placebo-treated patients. The between group difference was not statistically significant but revealed 1.5 headache-free days in favor of Botulinum toxin type-A treatment. There was a statistically significant difference was observed at day 180 endpoint for the secondary efficacy measure. A significantly higher percentage of Botulinum toxin type-A patients had a decrease from baseline of 50% or greater in the frequency of headache days per 30-day period at day 180 (32.7% vs. 15.0%, P=.027). The mean change from baseline in the frequency of headaches per 30 day period at day 180 was -6.1 for Botulinum toxin type-A patients vs. -3.1 for the placebo patients (P=.013). Only 4 of 173 Botulinum toxin type-A patients (2.3%) discontinued the study due to adverse events (59). From the data collected in this study, the researchers concluded that Botulinum toxin type-A treatment resulted in patients having, on average, approximately seven more headache free days compared to baseline.

Although at the primary time point the Botulinum toxin type-A treatment resulted in a 1.5 between-group difference compared to placebo and the difference was determined to be not statistically significant. The treatment met secondary efficacy outcome measures, including the percentage of patients experiencing a 50% or more decrease in the frequency of headache days in addition to statistically significant reductions in headache frequency. A follow up study using a subgroup analysis of the 11month, randomized double-blind, placebo-controlled study of Botulinum toxin type-A was later published in April of 2005. The objective of this study was to assess the efficacy and safety of Botulinum toxin type A for the prophylaxis of headaches in patients with chronic daily headache (CDH) without the confounding factor of concurrent prophylactic medications. This investigation involved data for patients who were not receiving simultaneous prophylactic headache medication and who constituted 64% of the full study population. This placebo-controlled study consisted of a 30 day baseline period during which headache frequency was monitored along with a 30 day single blind placebo run in period during which response to placebo was determined and a 9 month double blind treatment period during which patients received three treatment cycles (Botulinum toxin type-A or placebo) separated by 90 days (56). 228 patients from the original study group were not taking prophylactic medication and were included in this analysis. 117 patients received Botulinum toxin type-A and 111 patients received placebo injections. Mean age was 42.4 ± 10.90 years with a mean frequency of headaches per 30 days at baseline of 14.1 for the Botulinum toxin type-A group and 12.9 for the placebo group ( $P$ = .205). After two injection sessions, the maximum change in the mean frequency of headaches per 30 days was -7.8 in the Botulinum toxin type-A group compared with only -4.5 in the placebo

group ( $P$ = .032). There was a statistically significant between group difference of 3.3 headaches. The between group difference favoring Botulinum toxin type-A treatment continued to improve to 4.2 headaches after a third injection session ( $P$ = .023). Botulinum toxin type-A treatment at least halved the frequency of baseline headaches in over 50% of patients after three injection sessions compared to baseline. Statistically significant differences between Botulinum toxin type-A and placebo were evident for the change from baseline in headache frequency and headache severity for most time points from day 180 through day 270. Only 5 patients (4 patients receiving Botulinum toxin type-A treatment; 1 patient receiving placebo) discontinued the study due to adverse events and most treatment related events were transient and mild to moderate in severity. The researchers concluded that Botulinum toxin type-A is an effective and well-tolerated prophylactic treatment in migraine patients with CDH who are not using other prophylactic medications (56).

## Controversy

Although there have been well done studies that have indicated that BoNT has shown promise in cases of refractory migraine headache treatment and prophylaxis, not everyone is convinced that the evidence is worthy of FDA approval for routine use. The primary issue with acceptance of research results showing efficacy of Botulinum toxin type-A in the treatment of migraine headaches is that the largest studies were funded by Allergan, the company that produces BoNT. "Official Disability Guidelines" and "ODG" are trademarks of Work Loss Data Institute**.** The "Official Disability Guidelines" uses a comprehensive annual update process based on scientific medical literature review, survey data analysis, and expert panel validation to determine strength of recommendation regarding medical procedures. It was designed for use by providers, employers, insurance claims professionals, and state workers' compensation authorities. The large claims review centers use the ODG as a guide to authorize or deny requests for authorization of procedures on enrolled workers. According to the ODG, "the evidence is mixed for migraine headaches. This RCT found that both Botulinum toxin type-A (BoNT-A) and Divalproex sodium (DVPX) significantly reduced disability associated with migraine, and Botulinum toxin type-A had a favorable tolerability profile compared with DVPX. (Blumenfeld, 2008). In this RCT of episodic migraine patients, low-dose injections of BoNT-A into the frontal, temporal, and/or glabellar muscle regions were not more effective than placebo (Saper, 2007). Botulinum neurotoxin is probably ineffective in episodic migraine and chronic tension-type headache. (Naumann, 2008)". In the

referenced study by Blumenfeld, comparative evaluation of the efficacy and safety of Botulinum toxin type A and Divalproex sodium as prophylaxis in reducing disability and impact associated with migraine was done. This was a randomized, double-blind, single-center prospective study. Fifty-nine patients received either Botulinum toxin type-A 100 U/placebo-DVPX bid or placebo- Botulinum toxin type-A /DVPX 250 mg bid. Botulinum toxin type-A /placebo injections were given at Day 0 and at Month 3. Patients were evaluated at Months 1, 3, 6, and 9. Both treatments showed significant improvements in migraine disability scores and reductions in headache days and headache index. A trend of decreased headache severity was observed with Botulinum toxin type-A. A greater percentage of DVPX patients reported adverse events possibly related to treatment (DVPX 75.8% vs. Botulinum toxin type-A 50%, P = .04) and discontinued because of adverse events (DVPX 27.6% vs Botulinum toxin type-A 3.3%, P = .012) (61). The second referenced study was done by Saper et al in 2007. This was a randomized, double-blind, placebo-controlled study of 232 patients with a history of four to eight moderate to severe migraines per month, with or without aura. Patients were randomized to placebo or one of four Botulinum toxin type-A groups that received injections into different muscle regions in the frontal (10 U), temporal (6 U), glabellar (9 U), or all three areas (total dose 25 U). For 3 months following a single treatment, patients recorded migraine-related variables in a daily diary. Their results indicated that Botulinum toxin type-A and placebo produced comparable decreases from baseline in the frequency of migraines (P > or = 0.411). In general, no statistically significant differences were observed for any efficacy variable. The overall rates of adverse events or treatment related adverse events were similar among the groups. They concluded that low dose

injections of Botulinum toxin type-A into the frontal, temporal, and/or glabellar muscle regions were not more effective than placebo (62). The third referenced study was done by Naumann et al in 2008. A literature search was performed including MEDLINE and Current Contents for therapeutic articles relevant to Botulinum toxin type-A and the selected indications. They concluded by their research that Botulinum toxin type-A is probably ineffective in episodic migraine and chronic tension-type headache. There is presently no consistent or strong evidence to permit drawing conclusions on the efficacy of Botulinum toxin type-A in CDH mainly transformed migraine (63).

## Recent Data

In September 2008, Allergan announced that it had completed analyzing data of two Phase III clinical trials designed to evaluate the use of botulinum toxin type-A for the prophylactic treatment of headache in adults suffering from chronic migraine as defined by the criteria of chronic daily headaches. In the two Phase III clinical trials, patients were randomly assigned for treatment with botulinum toxin type-A or placebo injections every 12 weeks. The primary analysis was performed at week 24 following 2 treatment cycles. The two major efficacy measures evaluated in the trials were change from baseline in the number of headache episodes and number of headache days occurring in the 28 day period preceding the week 24 time point. In the first Phase III clinical trial, Allergan prospectively selected number of headache episodes as the primary endpoint for evaluation. Number of headache days was selected as the major secondary endpoint. Results from the first Phase III clinical trial indicated that although both the botulinum toxin type-A and placebo treatment groups showed a statistically significant improvement from baseline. There was no significant difference in the reduction of number of headache episodes between patients receiving botulinum toxin type-A and placebo. As in previous study outcomes, the study did show a decrease in number of headache days which is the FDA's preferred efficacy measure. This was significantly greater in patients receiving botulinum toxin type-A as compared to patients receiving placebo ($p=0.006$). The decrease in number of migraine or probable migraine days was also found to be significantly greater in patients treated with botulinum toxin type-A as compared to

patients receiving placebo (p=0.002). Based on the data from the first Phase III clinical trial, the primary endpoint for the second Phase III study was prospectively changed to number of headache days, with number of headache episodes changed to a secondary endpoint, before the data were unmasked. In the second Phase III study, the primary endpoint and key secondary endpoints showed statistically significant benefit of botulinum toxin type-A treatment over placebo injections. The patients treated with botulinum toxin type-A demonstrated a significantly greater decrease in both number of headache days ($p<0.001$) and number of headache episodes (p=0.003). As in the first Phase III trial, the second study also showed a decrease in number of migraine or probable migraine days that was significantly greater in patients treated with botulinum toxin type-A as compared to placebo ($p<0.001$). In both Phase III clinical trials, botulinum toxin type-A treatments were well tolerated in patients suffering from chronic migraine. Both studies used quality of life evaluation using the validated Headache Impact Test which is a migraine management tool to help identify the severity and frequency of migraine headaches. Patients receiving botulinum toxin type-A treatments scored statistically significantly higher improvement in quality of life when compared to patients receiving placebo injections ($p<0.001$ in both studies). Allergan is in the process of gaining approval from the FDA to add the use of botulinum toxin-A for treatment of chronic migraine headaches based on this new data. Other recent smaller studies sponsored by Allergan produced similar results (64).

## MIDAS Questinnaire

Despite the lack of support by the FDA, numerous practitioners as including those in some VA hospitals perform botulinum toxin-A injections for prophylactic treatment of refractory chronic megraine headaches. Both the Neurology Department at Bay Pines Hospital in St. Petersburg, Fl and the Neurology Department's Pain Management Clinic at James A Haley VA Hospital in Tampa, Fl provide this service. From observation and evaluation of the patients undergoing the procedure, it appeared that there was a general positive response to the treatment and overall patient satisfaction. Unfortunately there was no documentation to quantitate the effect on the patient's improvement in lost work days, ability to perform activities of daily living, increase or decrease in medication use as well as cost difference pre and post treatment and effect on activities of daily living. One of the tools for evaluation of the severity of a patient's disability due to the effects of migraine headaches is the Migraine Disability Assesment (MIDAS) questionairre. The MIDAS questionnaire was put together to help measure the impact migraine headaches have on the patient's life over the 3 months prior to the interview by the physician administering it. The primary intent was to assess headache-related disability with the aim of improving migraine care. Headache sufferers answer five questions scoring the number of days in the past 3 months related to activity limitations due to migraine. The internal consistency, test–retest reliability, and validity of the questionnaire were assessed in separate population based studies of migraine sufferers. The face validity, ease of use, and clinical utility of the questionnaire were evaluated in a group of 49 physicians who

independently rated disease severity and need for care in a diverse sample of migraine case histories. The test–retest Pearson correlation coefficient for the total MIDAS score was approximately 0.8. The MIDAS score was valid when compared with a reference diary based measure of disability. The overall correlation between MIDAS and the diary based measure was 0.63. The MIDAS score was also correlated with physicians' assessments of need for medical care ($r$ = 0.69). From studies completed to date, the MIDAS Questionnaire has been shown to be internally consistent, highly reliable, valid, and correlates with physicians' clinical judgment. These features support its suitability for use in clinical practice. Use of the MIDAS Questionnaire may improve physician patient communication about headache related disability and may favorably influence health care delivery for migraine patients (66). Though the questionnaire has been validated by the American Academy of Neurology, it only gives information regarding the severity of the patient's disability prior to care by the physician giving it. The questionnaire does not address other issues such as direct or indirect cost of treating migraine headaches. In a 2005 study done by Goldberg, migraine headaches were estimated to result in annual costs totaling as much as $17 billion in the United States (67). Most of the direct costs are for outpatient services such as medications, office visits, emergency department visits, laboratory/diagnostic services and management of treatment side effects. Indirect costs from lost productivity in the workplace, as previously discussed, add substantially to the total. The Triptan class of drugs, used for abortive treatment, account for the greatest portion of medication costs. Research suggests that a stratified care strategy, with initial therapy based on the patient's score on the MIDAS scale, is both clinically advantageous and more cost effective than stepped care strategies. It should be noted that the Triptans

are not interchangeable and costs as well as clinical outcomes may vary with different agents in this class. Migraine prophylaxis is aimed at preventing frequent attacks and the development of a long term condition that often incurs heavy costs for abortive treatment, diagnostic services, and medical care. Agents approved for migraine prophylaxis include those listed in the above previous discussion. As with abortive therapy, costs vary widely among these prophylactic agents. Of the total annual cost associated with migraine and its treatment, roughly $1.5 billion goes to medication with Triptans accounting for $1.18 billion with a mean cost per prescription of $160 (68). Focusing specifically on migraine headaches, another study found that the annual cost to employers exceeded $14.5 billion, of which $7.9 billion was due to absenteeism, $5.4 billion to diminished productivity, and $1.2 billion to medical costs (69). A small open label trial of Botulinum toxin was conducted in 5 patients with migraine headaches that were unresponsive to conventional antimigraine medications. Evaluation was done after 1 year of injections at 3 month intervals. The use of other migraine medications, as measured by the change in annual costs for other medications, had decreased from pretreatment levels. When the cost of the Botulinum toxin-A treatment itself was included, the total change in annual medication cost ranged from an increase of $648 to a decrease of $2717. All of the patients showed substantial clinical improvement with no reported adverse events. Migraine symptoms typically decreased within a few days after each injection and maximal effects were noted over the 2 months after treatment (70). A budgetary model provided a theoretical basis for predicting the cost outcome of selecting a given approach to migraine management. This model focused on the use of Botulinum toxin-A for prophylaxis in chronic migraine patients enrolled in a commercial managed care plan. The goal was to assess the impact

of a decision to allow the use of Botulinum toxin, in terms of cost effect for the plan as a whole. In calculating the cost of prophylaxis with Botulinum toxin, treatment at a standard interval of 3 months means that patients would receive 4 treatments per year. With the cost of each treatment given as $521.25, the yearly cost per patient is $2085, and the total yearly cost for 240 patients was $500,400. The model did not account for a decrease in emergency department visits and hospitalization as a result of effective migraine prophylaxis which would be expected to augment the savings. Offsetting these costs would be a reduction in the amount of headache medication used for abortive treatment (70). The final cost difference according to the study by Goldberg is that "in a plan with 1 million members, the savings associated with migraine prophylaxis using Botulinum toxin represents a change of less than 1 cent in overall cost per member per month ($76 360 divided by 12 million member months is a reduction of approximately $0.006 per member per month). The point, however, is not the insignificant change in cost, but that superior clinical outcomes in migraine management can be obtained with no increase in cost" (67). According to the results of his study, headache related visits to the office and emergency department were reduced by 32% and 49% respectively. These reductions in headache related visits resulted in a net savings of $18,757. The greatest clinical improvements were seen in patients whose conditions were most severe at baseline (72).

## Study Protocol

Having an interest in the patient's response to treatment with Botulinum toxin-A for migraine headache prophylaxis, this study utilized the questions in the MIDAS questionnaire with a slight modification to assess the patient's post treatment response. In addition to the original 7 questions on the questionnaire, additional information regarding medication usage pre and post treatment as well as assessment of functional ability pre and post and number of treatments. The study is designed as a cross sectional survey of patients currently undergoing the procedure at James A. Haley VA Medical Center Department of Neurology Pain Clinic and Bay Pines VA Hospital Department of Neurology outpatient clinic. Inclusion criteria were patients age 21 – 65 who had received at least 2 treatments. The patients currently undergoing the treatment with Botulinum toxin-A were pre screened by each department, on initial evaluation when first presenting to each clinic, to fit the criteria of chronic daily headaches as previously referenced and demonstrated a history of failure to other standard treatment protocols. Since the standard time between each treatment is typically 3-4 months, the questionnaire was to be administered over a 60 day period once initiated to prevent duplication of patient responses. No personal health information was required on the questionnaire and exemption was granted for informed consent and HIPPA requirements. The study objective is to assess patient reported efficacy of Botulinum toxin-A for the prophylaxis of Migraine headaches in patients with frequent Migraine headaches prior to initiation of treatment with Botulinum toxin-A compared to post treatment. The research plan as

previously discussed is to present questions addressing the patient status prior to the initiation of treatment as well as post treatment. Patient quality of life change, duration and frequency headache improvement are the primary focus. Other considerations included the cost difference between the previous use of other treatment and the periodic treatment with botulinum toxin-A. Methodology is a cross sectional study utilizing a questionnaire consisting of a modified Migraine Disability Assessment (MIDAS) questions were given to patients by the principle investigator or a significant member of the study who has undergone the required privacy training. Qualified patients are those who had received at least two series of injections. New patients who have not yet received treatment are excluded. The patients are currently under treatment at both Bay Pines VA neurology in St Petersburg, Fl and James A Haley VA pain clinic in Tampa, Fl. Patients who reported chronic Migraine headaches and were refractory to previous treatment methods were screened and placed in programs utilizing intramuscular injection of Botulinum toxin-A at standard points on the face, Temporalis muscle and paracervical muscles. The study's anticipated impact and significance relate to the fact that **p**atients that are debilitated by recurrent chronic migraine headaches suffer loss of productive time at work and home. Treatment with Botulinum toxin-A may results in significant relief allowing fewer days lost at work and improved quality of life. There may be significant cost saving if treatment results in discontinuation of other medications previously used for treatment of migraine headaches or decreased use of hospital and emergency department facilities. This study utilizes a questionnaire consisting of a modified Migraine Disability Assessment (MIDAS) questions will be given to patients who had received more than one series of injections. Included in the study are Male or

Female veterans age 21 – 65 currently under treatment with Botulinum toxin-A for migraine headache prophylaxis. Exclusion criteria consist of patients less than 21 years of age, initial treatment, over 65 years of age or physician clinical judgment for exclusion. Questionnaire filled out by the patient or by one of the attending physicians with proper privacy training with no personal health information on the form and voluntary participation as outlined on the cover sheet. Statistical analysis through patient response to a standardized questionnaire with weighted responses. Classification is based on existing patients currently undergoing care at the 2 neurology clinics who have already been screened to qualify for the procedure by the respective departments. The study is designed to extend no longer than 60 days following the start of initiating the questionnaire to prevent duplication of responses. This is assured since the patient treatment is no more frequent than every 90 – 120 days.

## Data Collection and Analysis

Patients at both James A Haley VA Department of Neurology Pain Clinic and Bay Pines Neurology Clinic who were currently undergoing treatment for migraine headaches with Botulinum toxin-A were randomly presented with the survey. The patients were screened per protocol to meet the criteria for the study. Since the patients were already undergoing treatment with Botulinum toxin-A for persistent refractory migraine headaches, they were already presumed to fit the definition of chronic daily headaches. Due to unplanned inconsistency in offering the questionnaire to the patients, the qualified respondents were randomly chosen and answered the survey. A total of 46 patients were surveyed at both Bay Pines VA and James A Haley VA. 19 patients were being treated at Bay Pines VA Neurology Clinic and 27 were under care at James A Haley VA Department of Neurology Pain Clinic. Of the 46 total patients surveyed, 10 were female and 36 were male. Due to IRB concerns at Bay Pines VA, the age variable was not recorded on surveys that were filled out in the Neurology Department there. Gender was recorded at both facilities as previously noted. The questions were graded according to responses to days affected by headache for 3 months prior to initiation of treatment and compared to responses of the same question modified to reflect the patient's condition for 3 months following at least one treatment. The first question of the questionnaire relates to the affect of migraine headaches on the patient's work. The second question relates lost work productivity. Question three asks about the ability of the patient to do housework during their migraine episodes. Similarly question four relates to interference

and decreased ability to effectively do housework, but not prevent it, due to migraine episodes. The fifth question asks about how the headache would interfere with family or social events. The 2 following questions labeled A and B on the MIDAS questionnaire were designated as 6 and 7 on the study pre and post questionnaire. They request the patient's assessment of frequency of headaches in days over the previous three months and severity of headaches as graded on a scale of 1 – 10. The MIDAS grading system contains a scale from I – IV. For simplicity purposes and data analysis, these are designated as 1 – 4 when interpreting the responses on the questionnaire (Table 1). Responses to questions 1 – 5 are converted from number of days reported to appropriate MIDAS grading scores. Since cost of treatment is a component of this study, section 8 asks additional questions regarding use of medications for treatment of migraine headaches pre and post Botulinum toxin-A. Question 9 asks the patient to assess the quality of life prior to and after treatment with Botulinum toxin-A. The final question on the post treatment questionnaire refers to the total number of treatments that the patient has had.

| Table 1 | | |
|---|---|---|
| **Grade** | **Definition** | **Days** |
| **Grade 1** | **Minimal or Infrequent Disability** | **0-5** |
| **Grade 2** | **Mild or Infrequent Disability** | **6-10** |
| **Grade 3** | **Moderate Disability** | **11-20** |
| **Grade 4** | **Severe Disability** | **21+** |

## Results

The mean age of the patients surveyed was confined to responses from James A Haley VA only due to the previously mentioned issues with Bay Pines VA IRB. Among those surveyed, the mean age was 51.8 with a range from 30 to 65 years of age. The ratio of males to females surveyed at both facilities was 3.6:1. Comparisons of responses to questions 1- 9 were analyzed using paired T-test, with the patient's pre-treatment status as the control, and Wilcoxon Signed Ranks Test. In Table 2 we see the results of paired samples statistics for questions 1 – 5. In response to question 1 regarding disability relating to the frequency of lost work days, the mean level of disability as indicated by the MIDAS score is reduced overall for the 46 respondents from a score of Grade 2 to Grade 1 with a mean reduction of .957 (Table 4). 95% confidence interval was .626 to 1.288 with a T-score of 5.82. When evaluating the results by Wilcoxon Signed Ranks Test, the number of patients who indicated a reduction in overall disability days is equal to those who indicated no change (Table 13). In analyzing the effect on interference with productivity at work, response to question 2 resulted in an overall mean reduction from Grade 3 to Grade 1. There was a mean reduction of 1.391 with a 95% confidence interval of 1.051 to 1.731 and a T-score of 8.244. Wilcoxon Signed Ranks Test revealed 32 respondents indicated a reduction in disability with 14 respondents indicating no change. In order to evaluate the effect that migraine headaches have on activities of daily living, question 3 asks how often the patient was prevented from performing daily housework. Assessment of the responses reveals a reduction overall from Grade 3 to

Grade 1 with a mean reduction of 1.28 at a 95% confidence interval of .947 to 1.618 and a t-score of 7.707 (Table4). Wilcoxon Signed Ranks Test analysis indicated that there were 31 respondents that reported a reduction in disability days and 15 that indicated no change (Table 13). Overall days where productivity was diminished regarding activities of daily living were addressed in question 4. The response indicated that there was an overall reduction from Grade 3 to Grade 1with a mean reduction of 1.457 at a 95% confidence interval of 1.088 to 1.825 with a t score of 7.954. Wilcoxon Signed Ranks Test analysis indicated 32 respondents had a reduction in MIDAS score while 13 had no change and 1 patient reported an actual increase in MIDAS score. The effect on social life and family activities is another area of concern which is addressed in question 5. According to the respondents there was a reduction in disability score from Grade 3 to Grade 1 with a mean reduction of 1.174 at 95% confidence interval of .829 to 1.519 with a T-score of 6.860. Wilcoxon Signed Ranks Test analysis reveals 28 respondents with a reduction in MIDAS score and 18 with no change in social or family activities. Question 6 asks the patient to record how many headaches they had in the 3 months prior to initiation of treatment and 3 months prior to the questionnaire post botulinum toxin-A treatment. Analysis of the responses demonstrates that there is a mean reduction of 41.957 headache days with a 95% confidence interval of 32.936 to 50.977 and a T-score of 9.368(Table 7). Wilcoxon Signed Ranks Test analysis reveals 42 patients reporting a reduction in frequency of headaches and 4 reporting no change (Table 16). Patients were asked to rate the severity of their headaches in question 7 based upon a standard scale of 0 – 10 with 0 being no pain and 10 being pain as bad as it could be. Analysis of the responses shows that there is an overall reduction of pain scores from a mean of 8.85

prior to treatment to 5.09 post treatment (Table 5) giving a mean reduction of 3.76 at a 95% confidence interval of 3.03 to 4.49 with a T-score of 10.368 (Table 5-7) . Wilcoxon Signed Ranks Test analysis reveals 40 patients reporting a reduction in the severity of their headaches, 1 reporting an increase in severity and 5 indicating no change in headache severity (Table 16). There is a lot of variability when evaluating medication usage. The type of medication used can vary greatly in price and frequency of usage. To simplify this, medications were placed on general categories. Weekly acetaminophen usage, as reflected in Tables 8-10, appeared to be reduced post treatment from a mean of 11.74 to 2.20 (Table 8) with a mean reduction of 9.04 at a 95% confidence interval between 1.476 to 16.611 and a T-score of 2.407 (Table 10). A breakdown of usage by Wilcoxon Signed Ranks Test analysis reveals 18 patients reporting a reduction, 26 patients indicating no change and 2 patients indicating an increase in usage (Table 17). General use of NSAIDs also showed reduction in use post treatment from a mean of 12.67 to 1.91 with a mean reduction of 10.761 at a 95% confidence interval between 4.518 to 17.004 and a T-score of 3.471. Wilcoxon Signed Ranks Test analysis indicates 20 patients reported a decrease in use, 1 increase in usage and 25 with no change in use. Use of opiates showed a decrease from a mean of 7.80 to 3.39 with a mean reduction of 4.413 at a 95% confidence interval between 1.743 to 7.083 and a T-score of 3.329. Wilcoxon Signed Ranks Test analysis shows 19 patients with a decrease in weekly use, 2 with an increase and 25 with no change in weekly use. Weekly Triptan use was reduced from a mean of 1.22 to .52 with a mean reduction of .696 at a 95% confidence interval of 2.24 to 1.168 and a T-score of 2.968. Wilcoxon Signed Ranks Test analysis reveals 14 patients reporting a decrease, 1 reporting an increase and 31 with no change (Table 18).

Response to use of psychotropic medications for treatment of migraine headaches showed a mean reduction from 3.54 to 1.24 with a mean reduction of 2.28 at a confidence interval of .528 to 3.983 and a T-score of 2.704. Wilcoxon Signed Ranks Test analysis indicates 11 patients with an increase in weekly use and 35 with no change. Other medications can consist of a wide variety including Ergotamines and Tramadol. The responses from the 46 patients reveal a mean reduction in weekly use from 2.54 to 1.70 with a mean reduction of .848 at a 95% confidence interval of -1.351 to 3.047 and a T-score of .776. Wilcoxon Signed Ranks Test analysis shows 9 patients reporting a reduction, 2 with an increase in use and 35 with no change in weekly usage. Overall quality of life showed an increase from a mean score of 3.20 to 7.17 (Table 11) with a mean improvement of 3.978 at a 95% confidence interval of -4.746 to -3.210 and a T-score of -10.433 (Table 13). Wilcoxon Signed Ranks Test analysis shows 1 patient indicating a decrease in quality of life, 41 indicating an improvement and 4 with no change (Table 19). Of the 46 patients responding to the questionnaire, 40 responded to the final question of number of treatments. The mean of those who responded was 10.2. Figures 1 – 14 graphically represent the pre and post responses of each patient to the questions on the survey.

**Paired Sample Tests**

| Table 2 | | Paired Samples Statistics | | | |
|---|---|---|---|---|---|
| | | Mean | N | Std. Deviation | Std. Error Mean |
| Pair 1 | Pre1 | 2.20 | 46 | 1.222 | .180 |
| | Post1 | 1.24 | 46 | .766 | .113 |
| Pair 2 | Pre2 | 2.72 | 46 | 1.167 | .172 |
| | Post2 | 1.33 | 46 | .790 | .117 |
| Pair 3 | Pre3 | 2.67 | 46 | 1.194 | .176 |
| | Post3 | 1.39 | 46 | .930 | .137 |
| Pair 4 | Pre4 | 2.72 | 46 | 1.223 | .180 |
| | Post4 | 1.26 | 46 | .648 | .095 |
| Pair 5 | Pre5 | 2.46 | 46 | 1.295 | .191 |
| | Post5 | 1.28 | 46 | .688 | .102 |

| Table 3 | Paired Samples Correlations | | | |
|---|---|---|---|---|
| | | N | Correlation | Sig. |
| Pair 1 | Pre1 & Post1 | 46 | .448 | .002 |
| Pair 2 | Pre2 & Post2 | 46 | .367 | .012 |
| Pair 3 | Pre3 & Post3 | 46 | .458 | .001 |
| Pair 4 | Pre4 & Post4 | 46 | .235 | .115 |
| Pair 5 | Pre5 & Post5 | 46 | .450 | .002 |

**Table 4** **Paired Samples Test**

| | | Paired Differences | | | | | t | df | Sig. (2-tailed) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% Confidence Interval of the Difference | | | | |
| | | Mean | Std. Deviation | Std. Error Mean | Lower | Upper | | | |
| Pair 1 | Pre1 - Post1 | .957 | 1.115 | .164 | .626 | 1.288 | 5.820 | 45 | .000 |
| Pair 2 | Pre2 - Post2 | 1.391 | 1.145 | .169 | 1.051 | 1.731 | 8.244 | 45 | .000 |
| Pair 3 | Pre3 - Post3 | 1.283 | 1.129 | .166 | .947 | 1.618 | 7.707 | 45 | .000 |
| Pair 4 | Pre4 - Post4 | 1.457 | 1.242 | .183 | 1.088 | 1.825 | 7.954 | 45 | .000 |
| Pair 5 | Pre5 - Post5 | 1.174 | 1.161 | .171 | .829 | 1.519 | 6.860 | 45 | .000 |

**Table 5** **Paired Samples Statistics**

| | | | Mean | N | Std. Deviation | Std. Error Mean |
|---|---|---|---|---|---|---|
| Pair 1 | Pre6 | 62.89 | 62.89 | 46 | 29.411 | 4.336 |
| | Post6 | 20.93 | 20.93 | 46 | 25.404 | 3.746 |
| Pair 2 | Pre7 | 8.85 | 8.85 | 46 | 1.095 | .161 |
| | Post7 | 5.09 | 5.09 | 46 | 2.439 | .360 |

| **Table 6** | **Paired Samples Correlations** | | | |
|---|---|---|---|---|
| | | N | Correlation | Sig. |
| Pair 1 | Pre6 & Post6 | 46 | .393 | .007 |
| Pair 2 | Pre7 & Post7 | 46 | .205 | .172 |

| **Table 7** | **Paired Samples Test** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Paired Differences | | | | | | | |
| | | | | | 95% Confidence Interval of the Difference | | | | |
| | | Mean | Std. Deviation | Std. Error Mean | Lower | Upper | t | df | Sig. (2-tailed) |
| Pair 1 | Pre6 - Post6 | 41.957 | 30.376 | 4.479 | 32.936 | 50.977 | 9.368 | 45 | .000 |
| Pair 2 | Pre7 - Post7 | 3.761 | 2.460 | .363 | 3.030 | 4.491 | 10.368 | 45 | .000 |

| **Table 8** | **Paired Samples Statistics** | | | | |
|---|---|---|---|---|---|
| | | Mean | N | Std. Deviation | Std. Error Mean |
| Pair 1 | Tyl Pre | 11.74 | 46 | 24.848 | 3.664 |
| | Tyl Post | 2.70 | 46 | 6.073 | .895 |
| Pair 2 | NSAID Pre | 12.67 | 46 | 21.170 | 3.121 |
| | NSAID Post | 1.91 | 46 | 4.273 | .630 |
| Pair 3 | Opiate Pre | 7.80 | 46 | 11.299 | 1.666 |
| | Opiate Post | 3.39 | 46 | 8.131 | 1.199 |
| Pair 4 | Triptan Pre | 1.22 | 46 | 2.021 | .298 |
| | Triptan Post | .52 | 46 | .752 | .111 |
| Pair 5 | PSY Pre | 3.52 | 46 | 6.595 | .972 |
| | Psy Post | 1.24 | 46 | 3.484 | .514 |
| Pair 6 | Other Pre | 2.54 | 46 | 6.735 | .993 |
| | Other Post | 1.70 | 46 | 6.759 | .997 |

| **Table 9** | **Paired Samples Correlations** | | | |
|---|---|---|---|---|
| | | N | Correlation | Sig. |
| Pair 1 | Tyl Pre & Tyl Post | 46 | .016 | .914 |
| Pair 2 | NSAID Pre & NSAID Post | 46 | .135 | .371 |
| Pair 3 | Opiate Pre & Opiate Post | 46 | .615 | .000 |
| Pair 4 | Triptan Pre & Triptan Post | 46 | .698 | .000 |
| Pair 5 | PSY Pre & Psy Post | 46 | .497 | .000 |
| Pair 6 | Other Pre & Other Post | 46 | .398 | .006 |

**Table 10** **Paired Samples Test**

| | | Paired Differences | | | | | t | df | Sig. (2-tailed) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% Confidence Interval of the Difference | | | | |
| | | Mean | Std. Deviation | Std. Error Mean | Lower | Upper | | | |
| Pair 1 | Tyl Pre - Tyl Post | 9.043 | 25.483 | 3.757 | 1.476 | 16.611 | 2.407 | 45 | .020 |
| Pair 2 | NSAID Pre - NSAID Post | 10.761 | 21.024 | 3.100 | 4.518 | 17.004 | 3.471 | 45 | .001 |
| Pair 3 | Opiate Pre - Opiate Post | 4.413 | 8.990 | 1.326 | 1.743 | 7.083 | 3.329 | 45 | .002 |
| Pair 4 | Triptan Pre - Triptan Post | .696 | 1.590 | .234 | .224 | 1.168 | 2.968 | 45 | .005 |
| Pair 5 | PSY Pre - Psy Post | 2.283 | 5.726 | .844 | .582 | 3.983 | 2.704 | 45 | .010 |
| Pair 6 | Other Pre - Other Post | .848 | 7.406 | 1.092 | -1.351 | 3.047 | .776 | 45 | .442 |

**Table 11 Paired Samples Statistics**

| | | Mean | N | Std. Deviation | Std. Error Mean |
|---|---|---|---|---|---|
| Pair 1 | PreQual | 3.20 | 46 | 1.614 | .238 |
| | PostQual | 7.17 | 46 | 2.069 | .305 |

**Table 12 Paired Samples Correlations**

| | | N | Correlation | Sig. |
|---|---|---|---|---|
| Pair 1 | PreQual & PostQual | 46 | .030 | .846 |

**Table 13 Paired Samples Test**

| | | Paired Differences | | | | | t | df | Sig. (2-tailed) |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean | Std. Deviation | Std. Error Mean | 95% Confidence Interval of the Difference | | | | |
| | | | | | Lower | Upper | | | |
| Pair 1 | PreQual - PostQual | -3.978 | 2.586 | .381 | -4.746 | -3.210 | -10.433 | 45 | .000 |

**Wilcoxon Signed Ranks Test**

| **Table 14:** | **Ranks** | | | |
|---|---|---|---|---|
| | | N | Mean Rank | Sum of Ranks |
| Post1 – Pre1 | Negative Ranks | 23[a] | 12.00 | 276.00 |
| | Positive Ranks | 0[b] | .00 | .00 |
| | Ties | 23[c] | | |
| | Total | 46 | | |
| Post2 – Pre2 | Negative Ranks | 32[d] | 16.50 | 528.00 |
| | Positive Ranks | 0[e] | .00 | .00 |
| | Ties | 14[f] | | |
| | Total | 46 | | |

a. Post1 < Pre1; b. Post1 > Pre1; c. Post1 = Pre1

d. Post2 < Pre2; e. Post2 > Pre2; f. Post2 = Pre2

| **Test Statistics[b]** | | |
|---|---|---|
| | Post1 - Pre1 | Post2 - Pre2 |
| Z | -4.256[a] | -5.004[a] |
| Asymp. Sig. (2-tailed) | .000 | .000 |
| a. Based on positive ranks. b. Wilcoxon Signed Ranks Test | | |

**Table 15: Ranks**

| | | N | Mean Rank | Sum of Ranks |
|---|---|---|---|---|
| Post3 - Pre3 | Negative Ranks | 31[a] | 16.00 | 496.00 |
| | Positive Ranks | 0[b] | .00 | .00 |
| | Ties | 15[c] | | |
| | Total | 46 | | |
| Post4 - Pre4 | Negative Ranks | 32[d] | 17.36 | 555.50 |
| | Positive Ranks | 1[e] | 5.50 | 5.50 |
| | Ties | 13[f] | | |
| | Total | 46 | | |
| Post5 - Pre5 | Negative Ranks | 28[g] | 14.50 | 406.00 |
| | Positive Ranks | 0[h] | .00 | .00 |
| | Ties | 18[i] | | |
| | Total | 46 | | |

a. Post3 < Pre3; b. Post3 > Pre3; c. Post3 = Pre3; d. Post4 < Pre4; e. Post4 > Pre4; f. Post4 = Pre4; g. Post5 < Pre5; h. Post5 > Pre5; i. Post5 = Pre5

Test Statistics b

| | Post3 - Pre3 | Post4 - Pre4 | Post5 - Pre5 |
|---|---|---|---|
| Z | -4.928[a] | -4.983[a] | -4.687[a] |
| Asymp. Sig. (2-tailed) | .000 | .000 | .000 |

a. Based on positive ranks. b. Wilcoxon Signed Ranks Test

**Table 16: Ranks**

| | | N | Mean Rank | Sum of Ranks |
|---|---|---|---|---|
| Post6 - Pre6 | Negative Ranks | 42[a] | 21.50 | 903.00 |
| | Positive Ranks | 0[b] | .00 | .00 |
| | Ties | 4[c] | | |
| | Total | 46 | | |
| Post7 - Pre7 | Negative Ranks | 40[d] | 21.38 | 855.00 |
| | Positive Ranks | 1[e] | 6.00 | 6.00 |
| | Ties | 5[f] | | |
| | Total | 46 | | |

a. Post6 < Pre6; b. Post6 > Pre6; c. Post6 = Pre6; d. Post7 < Pre7; e. Post7 > Pre7; f. Post7 = Pre7

Test Statistics b

| | Post6 - Pre6 | Post7 - Pre7 |
|---|---|---|
| Z | -5.647[a] | -5.521[a] |
| Asymp. Sig. (2-tailed) | .000 | .000 |

a. Based on positive ranks. b. Wilcoxon Signed Ranks Test

**Table 17: Ranks**

| | | N | Mean Rank | Sum of Ranks |
|---|---|---|---|---|
| Tyl Post - Tyl Pre | Negative Ranks | 18[a] | 10.11 | 182.00 |
| | Positive Ranks | 2[b] | 14.00 | 28.00 |
| | Ties | 26[c] | | |
| | Total | 46 | | |
| NSAID Post - NSAID Pre | Negative Ranks | 20[d] | 11.50 | 230.00 |
| | Positive Ranks | 1[e] | 1.00 | 1.00 |
| | Ties | 25[f] | | |
| | Total | 46 | | |
| Opiate Post - Opiate Pre | Negative Ranks | 19[g] | 11.00 | 209.00 |
| | Positive Ranks | 2[h] | 11.00 | 22.00 |
| | Ties | 25[i] | | |
| | Total | 46 | | |

a. Tyl Post < Tyl Pre; b. Tyl Post > Tyl Pre; c. Tyl Post = Tyl Pre; d. NSAID Post < NSAID Pre; e. NSAID Post > NSAID Pre; f. NSAID Post = NSAID Pre; g. Opiate Post < Opiate Pre; h. Opiate Post > Opiate Pre; i. Opiate Post = Opiate Pre.

Test Statistics b

| | Tyl Post - Tyl Pre | NSAID Post - NSAID Pre | Opiate Post - Opiate Pre |
|---|---|---|---|
| Z | -2.876[a] | -3.982[a] | -3.258[a] |
| Asymp. Sig. (2-tailed) | .004 | .000 | .001 |

a. Based on positive ranks. b. Wilcoxon Signed Ranks Test

**Table 18: Ranks**

| | | N | Mean Rank | Sum of Ranks |
|---|---|---|---|---|
| Triptan Post - Triptan Pre | Negative Ranks | 14[a] | 8.32 | 116.50 |
| | Positive Ranks | 1[b] | 3.50 | 3.50 |
| | Ties | 31[c] | | |
| | Total | 46 | | |
| Psy Post - PSY Pre | Negative Ranks | 11[d] | 6.00 | 66.00 |
| | Positive Ranks | 0[e] | .00 | .00 |
| | Ties | 35[f] | | |
| | Total | 46 | | |
| Other Post - Other Pre | Negative Ranks | 9[g] | 5.83 | 52.50 |
| | Positive Ranks | 2[h] | 6.75 | 13.50 |
| | Ties | 35[i] | | |
| | Total | 46 | | |

a. Triptan Post < Triptan Pre; b. Triptan Post > Triptan Pre; c. Triptan Post = Triptan Pre; d. Psy Post < PSY Pre; e. Psy Post > PSY Pre; f. Psy Post = PSY Pre; g. Other Post < Other Pre; h. Other Post > Other Pre; i. Other Post = Other Pre.

Test Statistics b

| | Triptan Post - Triptan Pre | Psy Post - Psy Pre | Other Post - Other Pre |
|---|---|---|---|
| Z | -3.255[a] | -3.207[a] | -1.746[a] |
| Asymp. Sig. (2-tailed) | .001 | .001 | .081 |

a. Based on positive ranks. b. Wilcoxon Signed Ranks Test

**Table 19: Ranks**

| | | N | Mean Rank | Sum of Ranks |
|---|---|---|---|---|
| PostQual - PreQual | Negative Ranks | 1[a] | 17.50 | 17.50 |
| | Positive Ranks | 41[b] | 21.60 | 885.50 |
| | Ties | 4[c] | | |
| | Total | 46 | | |

a. PostQual < PreQual; b. PostQual > PreQual; c. PostQual = PreQual

Test Statistics b

| | PostQual - PreQual |
|---|---|
| Z | -5.444[a] |
| Asymp. Sig. (2-tailed) | .000 |

a. Based on negative ranks. b. Wilcoxon Signed Ranks Test.

**Figure 1**

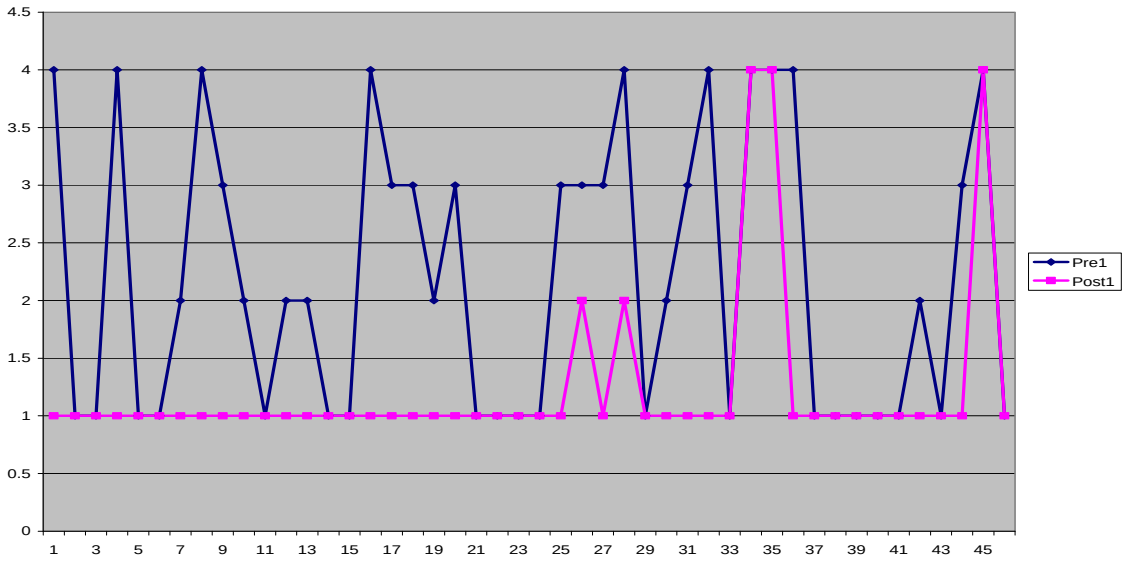



**Figure 2**

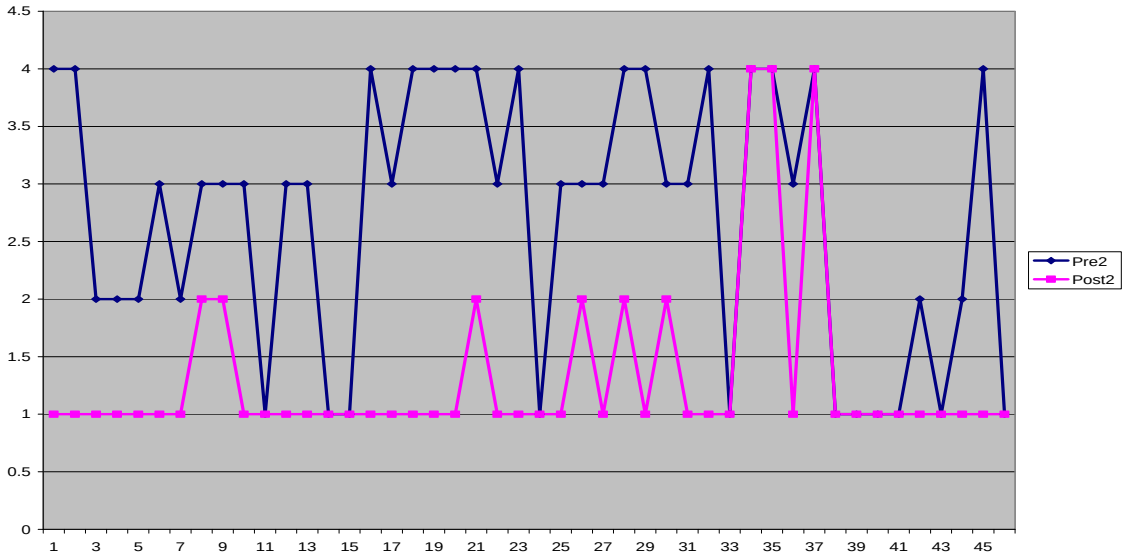


**Figure 3**

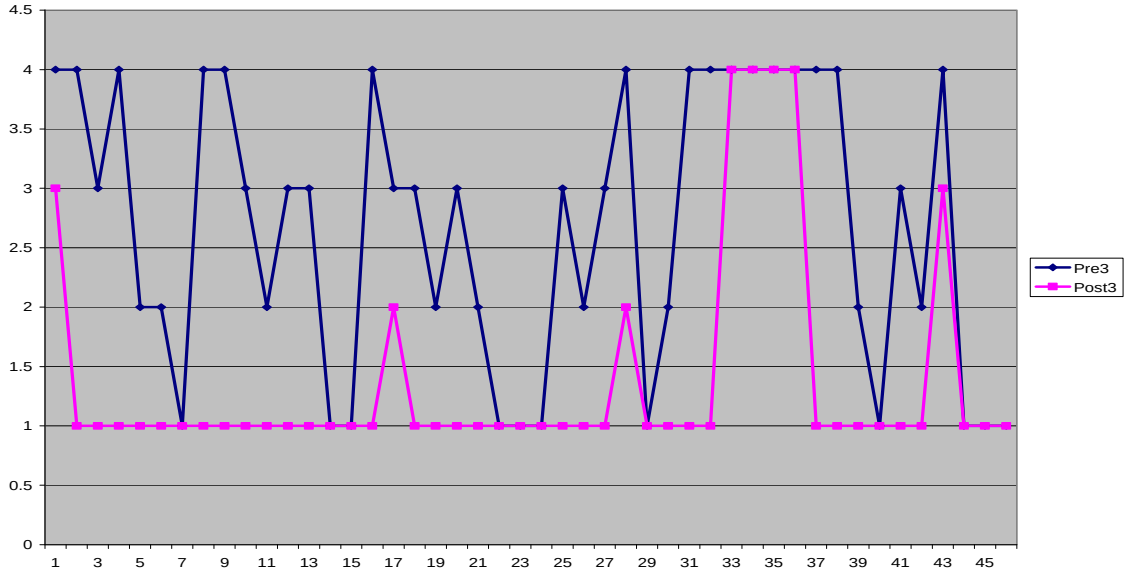



**Figure 4**

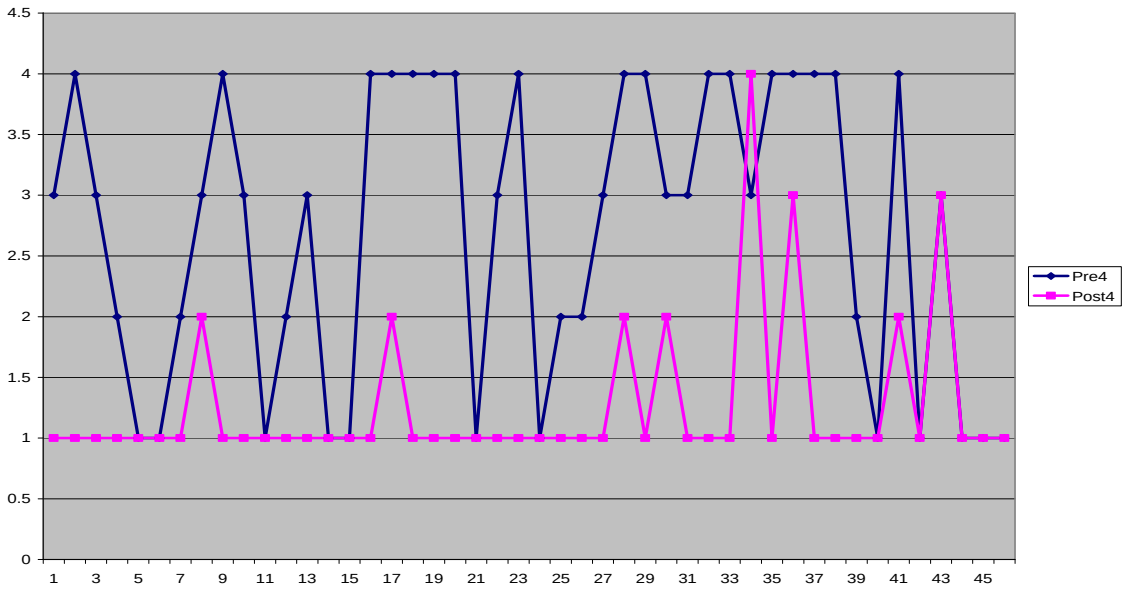


**Figure 5**

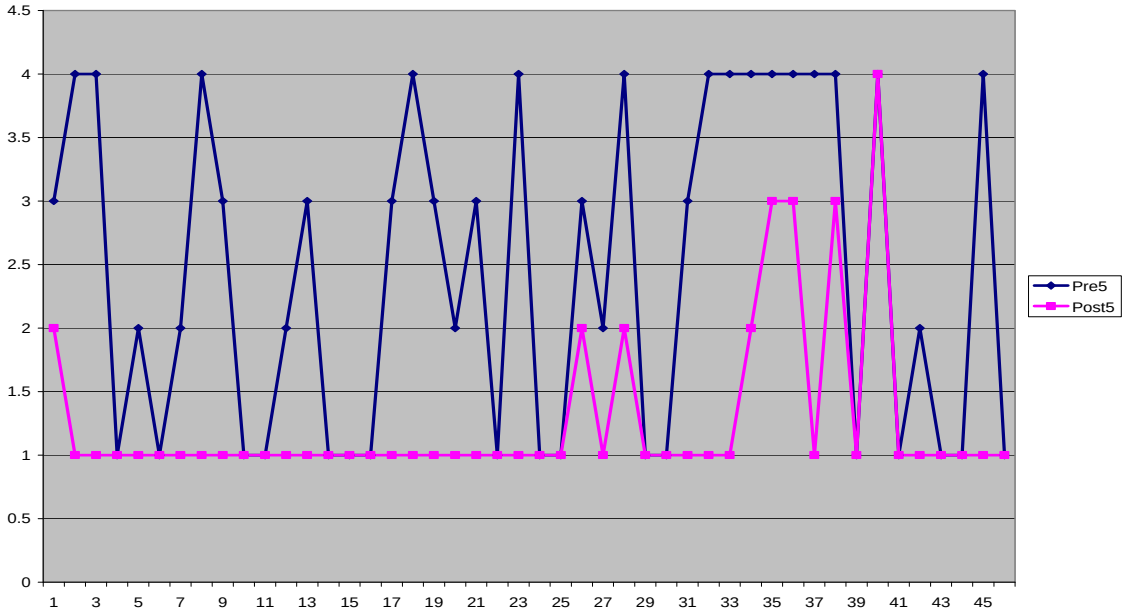



**Figure 6**

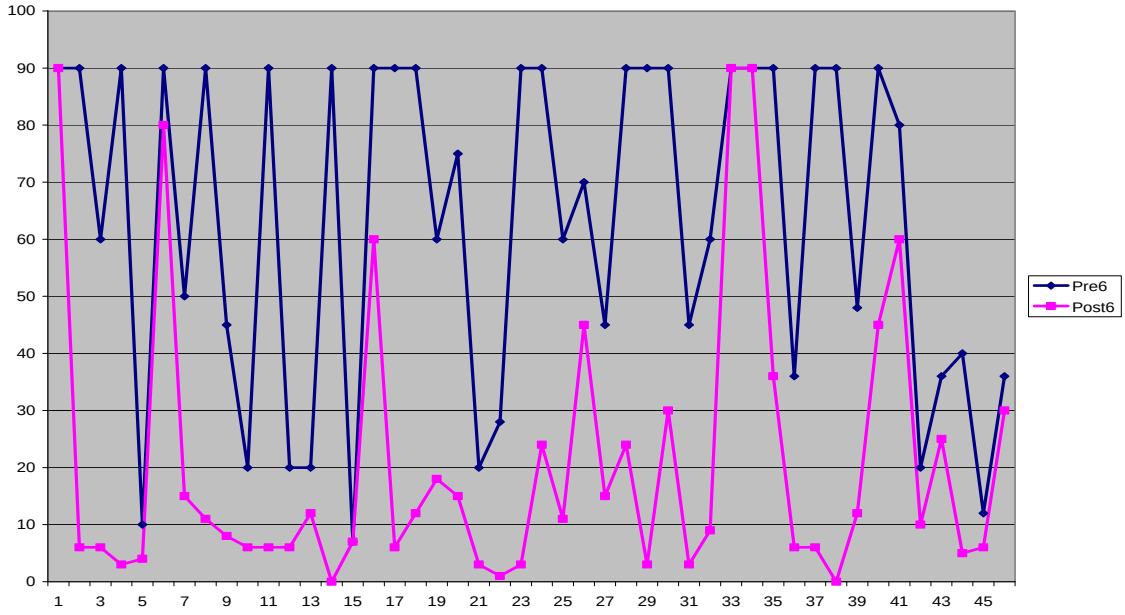


**Figure 7**

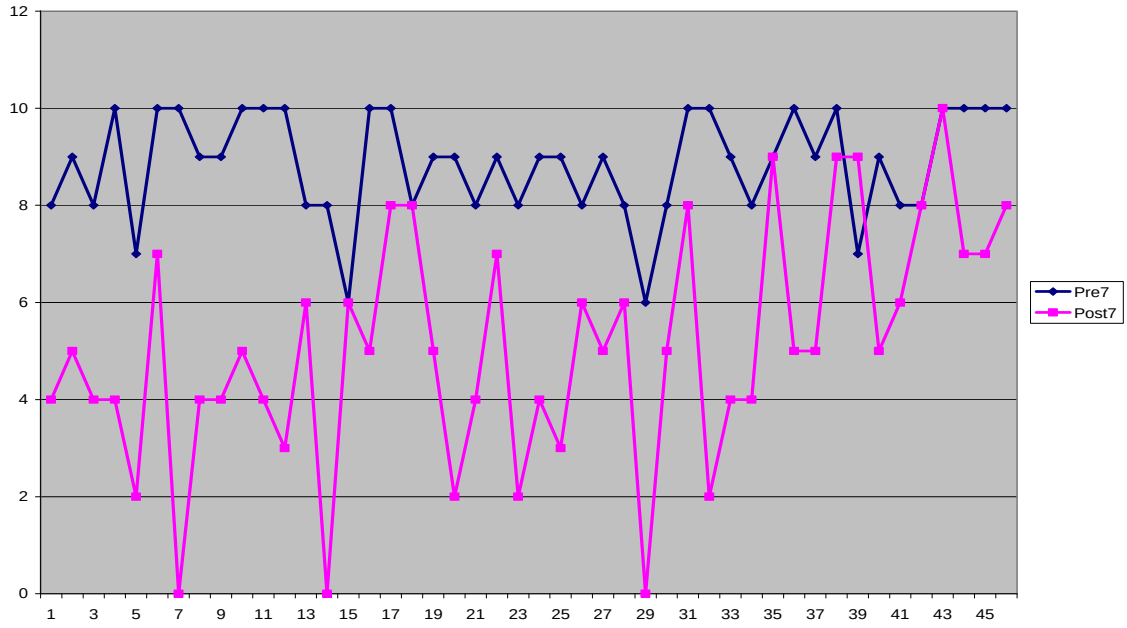



**Figure 8**

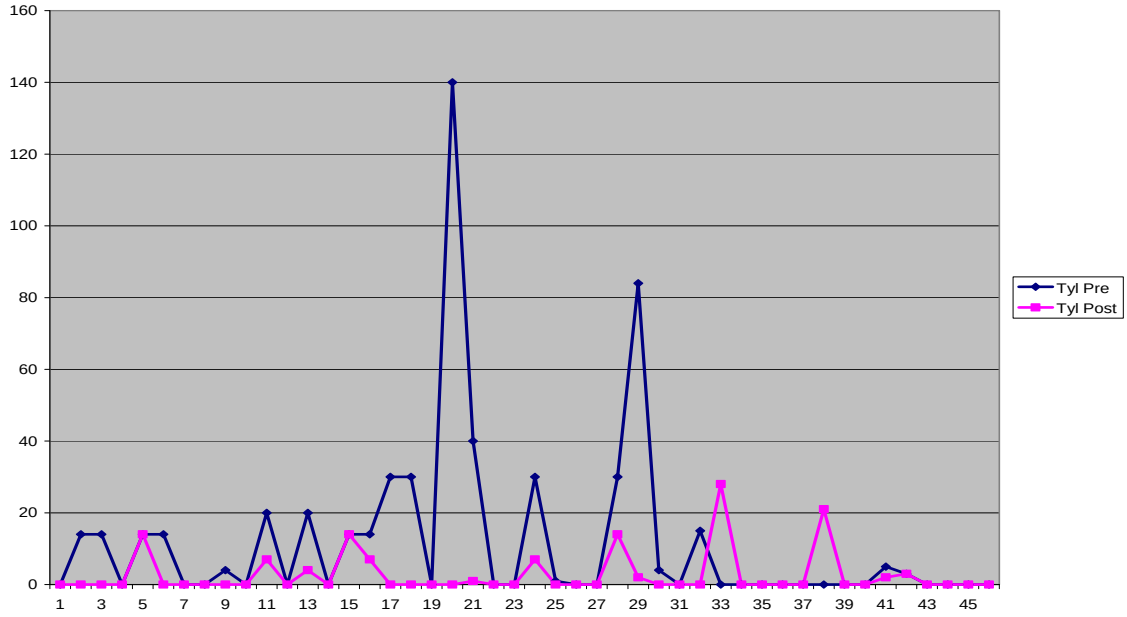


**Figure 9**

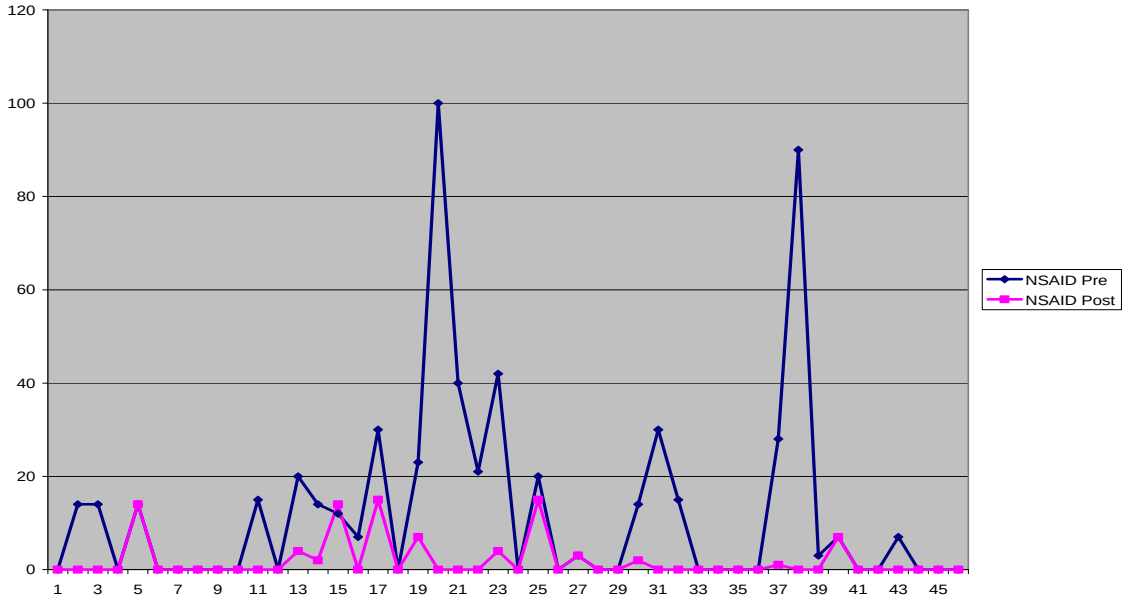



**Figure 10**

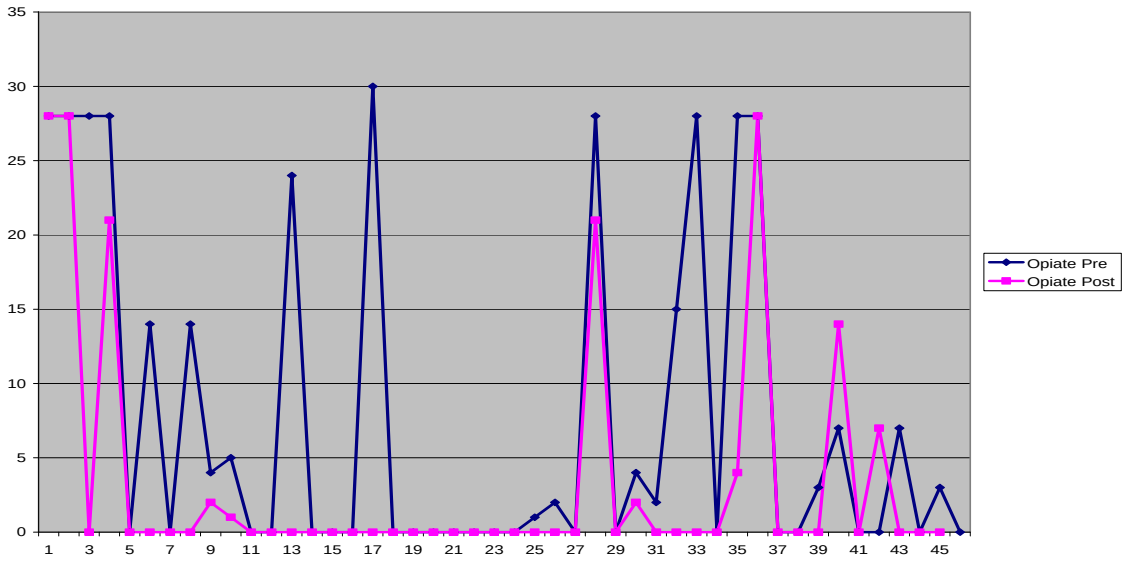


**Figure 11**

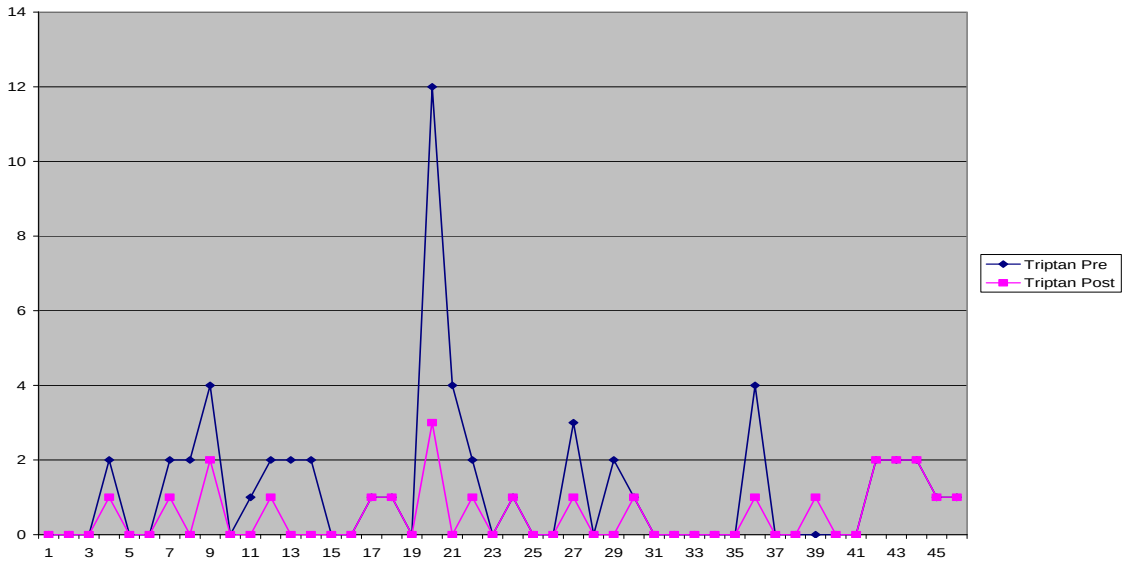



**Figure 12**

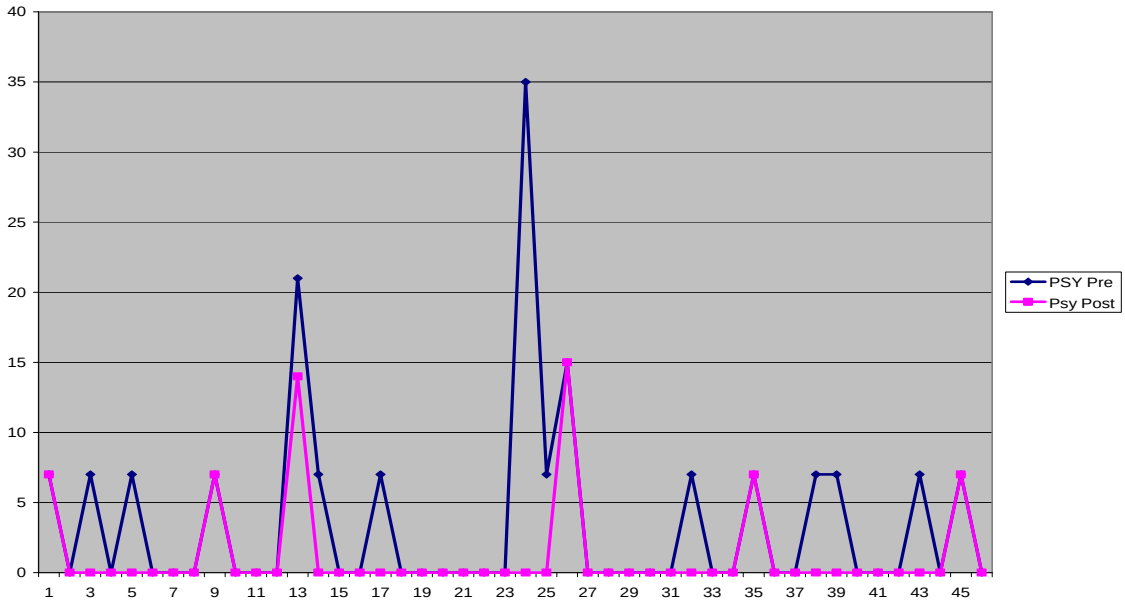


**Figure 13**

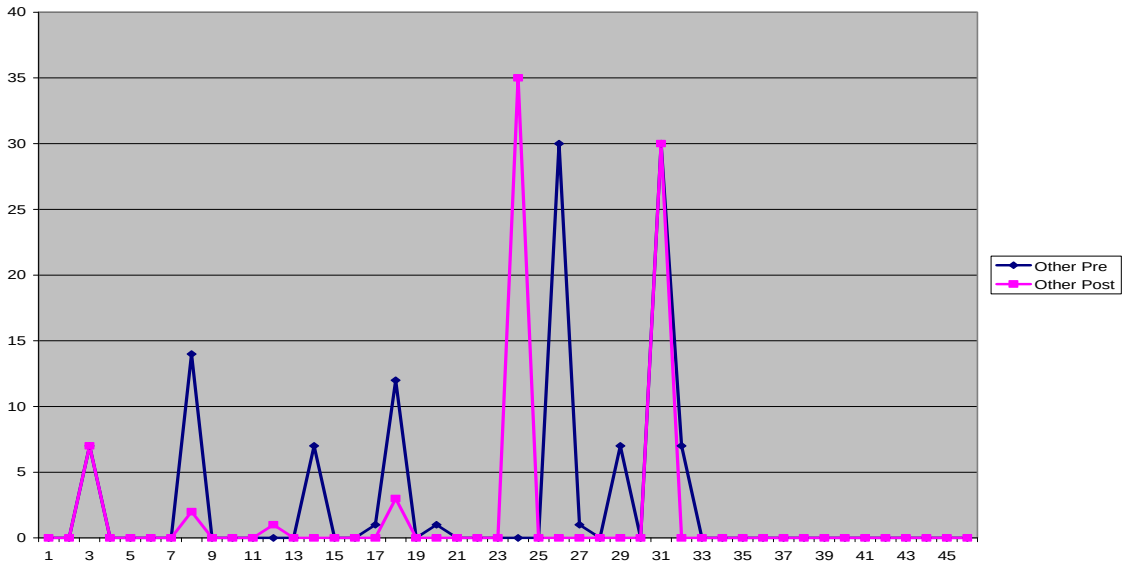
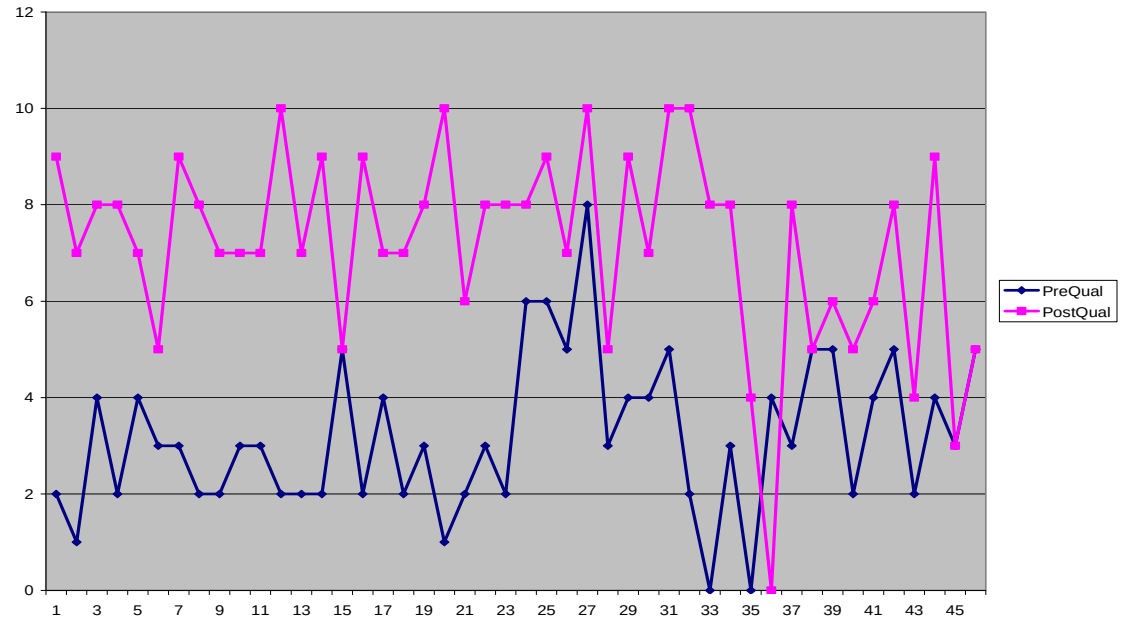



**Figure 14**



## Conclusion

According to the patients' response to this survey, it appears that there was an overall improvement in the patients' ability to do work, for those who were employed, as well as their ability to do activities of daily living post treatment with Botulinum toxin-A. From the patients' response there was an approximate 67% decrease in the mean frequency of headaches over the surveyed pre and post 3 month periods. The intensity of headaches also demonstrated a mean decrease from approximately 9/10 to 5/10 from pre to post treatment. When estimating the cost of treatment, prices for each class of medication were calculated using an estimated average for the prescription strength of each class of medication. The estimated cost of Acetaminophen 325mg is about $.17 per capsule. Having a mean reduction in weekly use of approximately 9 pills doesn't really amount to a tremendous cost saving and over a 3 month period it would translate to approximately $18.36 saved. Similarly inexpensive are NSAIDs. At an average price using the most commonly prescribed/recommended NSAIDs (Ibuprofen 800mg, Naproxen 500mg, Nabumetone 750mg and Fiorinal 50/325/40), the average price per pill is $1.66. There was a mean reduction of 10.76 pills per week according to the survey responses. This translates to a weekly reduction of $17.87 and a 3 month saving of approximately $214.36. Mean weekly opiate use reduction was 4.413. At and average cost of the most commonly prescribed narcotic analgesics (Hydrocodone, Oxycodone, Meperidine as well as combination with non narcotic analgesics) of $2.41 per pill, the overall savings for the 3 month period would be estimated at $127.62. The most expensive medications of this

survey were the Triptans. Using an average per dose price for the most commonly prescribed of this group (Maxalt, Imitrex and Zomig), the average price per oral dose was approximately $26.53. With a mean reduction of .696 per week at a 3 month time frame, the estimated cost saving would be $221.58. The use of psychotropic medications, such as Trazadone 100mg, Amitryptyline 50mg and Divalproex sodium 250mg, was estimated at an average price of $2.34 per pill. Calculation of 3 month use was reduced by a mean weekly drop of 2.253 results in a saving of $63.26. There are numerous other medications that are used to treat migraine headaches however for simplicity purposes I chose to evaluate Tramadol 50mg and Cafergot 1-100. The average price per dose for these two medications is approximately $2.67. With a mean weekly reduction of .848, the 3 month saving would translate to approximately $27.17. The cost of each treatment with Botulinum toxin A for the VA facilities participating in this study is about $400.00. There was a reported mean increase in overall quality of life from 3.20 to 7.17 on the scale of 0 (non functional) to 10 (excellent). When interviewing the patients the majority of those responding indicated overall satisfaction with their treatment. The mean number of treatments was 10.2.

## Discussion

When interpreting the results of the respondents to this survey, a few concerns come to mind. The first thought is that I was unable to evaluate responses from patients who may have had adverse response or stopped treatment due to lack of response. There is also some technical difficulty in ensuring that the response only involves information relating to migraine headache and not other chronic pain conditions that may also coexist. Also when evaluating pain medication usage, limiting responses only to those medications used for the treatment of migraine headaches proved challenging since some medications were used for other chronic pain conditions concurrently. It is difficult to get an accurate cost analysis since there is a tendency to have multiple prescription medications and over the counter medications used in efforts to treat and prevent chronic migraine headaches. Also the cost of the medications, particularly Triptans, will vary greatly according to the route administered. Another cost factor that was occasionally revealed by the respondents is the frequency of visits to the emergency room for treatment of migraine headaches. Though it was not evaluated by this study, some of the respondents did reveal frequent visits to the emergency room which they indicate were reduced or eliminated post treatment. Overall it appears that the use of Botulinum toxin-A in the treatment of migraine headaches does have some clinical value and can possibly be used in refractory cases to help increase the patients functional capacity and possibly reduce the cost of treatment by reducing multiple prescription medication use and reduce the frequency of visits to emergency rooms.

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