Traumatic Brain Injury and Neurodegenerative Disease: A Literature Review

By

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CERTIFICATE OF APPROVAL

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Honors Thesis

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Outline for Thesis

1. Thesis statement

2. Introduction

3. Traumatic brain injury (TBI)

    1. The symptoms of a TBI

    2. Second impact syndrome (SIS)

    3. The role of gender and age

    4. The role of genetics

4. Neurodegenerative disease

5. The correlation between TBI and neurodegenerative disease

6. Current and future advances in treating TBIs and neurodegenerative disease

7. Prevention and education of TBI's

8. Conclusion

Thesis Statement

One needs only to turn on the television to see the impact head trauma has had on us as a society. We see commercials for veterans coming home whom have suffered TBI's due to injuries in the line of battle. We see athletes suffering from the effects of neurodegenerative diseases such as chronic traumatic encephalopathy (CTE). Most of these symptoms are hidden, making it easy to sweep the problem under the rug, so to speak. As of late, we are hearing of major sports leagues such as the National Hockey League (NHL), National Football League (NFL), Major League Baseball (MLB), some mixed martial arts companies such as UFC, as well as professional wrestling companies such as World Wrestling Entertainment (WWE) taking the lead in prevention of head trauma. The past two years in particular we have seen more suspensions and fines in the NFL and NHL for intentional hits to the head which can cause a TBI. It is more difficult to take action against strong blows to the body, which can also cause a TBI, due to the nature of these sports, but we have a starting point with these major organizations. This is a problem we must address, and we must address it early. Failure to do so will only result in more suffering for those whom have suffered a brain injury (or in some instances multiple brain injuries) as well as those around them. Due to the changes in the brain, we do see emotional problems arise which is where we have seen irrational acts such as domestic violence, murders and suicides. If we do not address this problem, these acts will continue and it will become a vicious circle.

In my thesis, I plan to explain what a traumatic brain injury (TBI) is, as well as second impact syndrome (SIS), its symptoms, and the role age, gender and genetics play in not only suffering a TBI but the effects these factors play in recovery from the injury. I also plan on exploring what a neurodegenerative disease is and the role TBI's play in these diseases. I will

explore different treatment options, including the latest information on treatment that is in its early testing phases such as focused ultrasound, which has suggested a non-pharmaceutical way to treat neurodegenerative disease and possibly break up the plaques that accompany these diseases. Finally I will look at prevention of head trauma and what the future holds for research in the field of head trauma and neurodegenerative disease.

Through my thesis, I plan on showing that future research is needed as this is a rapidly evolving field. We are continually finding out new information on how the brain reacts to trauma both immediately following an injury as well as long term. Along with this we also are discovering new treatment methods. My hope would be that we could discover more non-pharmaceutical methods of treatment of TBI's in both the short term and long term. I personally have suffered numerous TBI's from wrestling professionally and suffer through many of the symptoms I will discuss. If my thesis helps even one other person not experience what I am now suffering from, then my thesis would be a success.

Introduction

Over the past several years we have seen a link between concussions, otherwise known as traumatic brain injury (TBI), emotional difficulties and suicide (Omalu, Bailes, Hammers, & Fitzsimmons, 2010). We also have seen an increase in suicides in both active military as well as veterans over the past several years. Suicides in the US Army reached the highest levels in 28 years in 2008 (Kuehn, 2009). TBI is common for both contact sport athletes and military members returning from battle, where we see "much of the initial controlled data on mTBI and concussions was gleaned from athletes who were at high risk for mild head trauma. With the multiple combat tours and the nature of warfare in Iraq and Afghanistan that are putting service members at risk for multiple concussive injuries, the lessons learned from the sports concussion literature are being applied to the military. While there are differences when TBIs occur in the combat setting, there are also similarities" (Kelly, Amerson, & Bath, 2012, p. 4). This has helped place more emphasis on head injuries. While we cannot definitively say there is a direct link between the two, there is something that many members of both of these demographics have in common. The tie that binds these groups, as mentioned above, would be TBI's. While I have discussed TBIs in the military, most of my research will focus on athletes. While many military members have suffered TBI's, they also suffer from Post-Traumatic Stress Disorder (PTSD) as well which has psychological symptoms that could skew our view of the symptoms suffered by those suffering from TBI's. Despite this fact, we can draw some correlation between the two. I plan to explore the causes, symptoms and prevention of TBI's as well as a correlation between TBI's and neurological diseases, including the cognitive and neurological deficits that accompany them.

TBI and Second Impact Syndrome

What exactly is a TBI? In a 2011 study by Schatz, Moder, Covassin, and Karpf (2011) they state that due to the increasing number of sports related TBI's, the Centers for Disease Control and Prevention has identified concussion (TBI) from sports an "epidemic" in the United States. The Centers for Disease Control and Prevention sums it up quite nicely by saying "a TBI is caused by a bump, blow, or jolt to the head that can change the way your brain normally works. Concussions can also occur from a fall or a blow to the body that causes the head and brain to move quickly back and forth" (Centers for Disease Control and Prevention, 2014). It is important to realize that not only blows to the head, but blows to the body can cause a TBI. "Animal studies were revealing neuropathological/histological changes in the brain stems of primates when subjected to acceleration, deceleration, rotational injuries, or mild traumatic brain injuries (mTBIs)" (Kelly, Amerson, & Bath, 2012, p. 1). There is no doubt that TBI's are a serious problem.

During an initial TBI we see brain swelling, but we also see a disruption of autoregulation of cerebral blood flow (Wetjen, Pichelmann, & Atkinson, 2010). In a study by Wetjen, Pichelmann, and Atkinson (2010) it was noted that during the initial head trauma, we see "induced cerebral autoregulation failure, with simultaneous catecholamine-induced marked blood pressure elevation" (Wetjen, Pichelmann, & Atkinson, 2010, p. 533) leading to rapid brain swelling. It stands to reason that it is "highly probable that the same events occur" (Wetjen et al., 2010, p. 553) in what is called second impact syndrome (SIS). "Cerebral autoregulation is best described as the "tone" the arterial tree assumes to either uniformly dilate or constrict to keep cerebral blood flow constant under normal conditions"(Wetjen et al., 2010, p. 553). Wetjen, Pichelmann, and Atkinson (2010) has found that this disruption in cerebral autoregulation occurs

in a linear fashion. In other words, the more serious the head trauma, the more serious the disruption to cerebral autoregulation will be. The release of catecholamine and its effects "occurs rapidly, within seconds of the head injury" (Wetjen et al., 2010, p. 554). We see a "rapid elevation in blood pressure" (Wetjen et al., 2010, p. 554) and heart rate. It has also been documented that there is a release of epinephrine and norepinephrine in cases of severe head trauma, which can have impacts on heart rate and blood pressure. It is suspected that these releases are linear as well (Wetjen et al., 2010, p. 554). It is this rapid swelling, release of catecholamine, increased blood pressure and heart rate, as well as the increase in epinephrine and norepinephrine that can be fatal. When a person suffers an initial TBI and then suffers a second TBI before completely healing from the initial injury, which is SIS, we see these effects occur again, increasing the chances of the injury being fatal.

Key to understanding exactly what a TBI is, is to understand the symptoms of a TBI. The "most widely used clinical TBI severity classification" (Bruns and Hauser, 2003, p. 8) system used is the Glasgow Coma Scale. The Mayo Clinic has some key symptoms on their website for both mild to moderate/severe TBI's. With mild TBI's we may see physical symptoms that range from loss of consciousness for a few seconds up to a few minutes. A loss of consciousness is not required for a diagnosis of a TBI though, as we do see some patients who have no loss of consciousness, but they may be in a state where they are dazed, confused or disoriented. Often times those who have suffered a mild TBI also will experience headaches, nausea or vomiting, fatigue or drowsiness, difficulty sleeping or sleeping more than usual, as well as dizziness or loss of balance. There are also sensory symptoms which accompany a mild TBI such as sensitivity to light or sound. Often the patient may have blurred vision, ringing in the ears, a bad taste in the mouth or changes in the ability to smell. There also may be cognitive or mental symptoms which

will be explored in greater detail later. This may include memory or concentration problems, mood changes or mood swings, as well as feeling depressed or anxious (The Mayo Clinic, 2014).

Moderate to severe TBI's include all of the symptoms of mild TBI's as well as additional symptoms that may appear in the hours or days following the initial TBI. Physical symptoms may include loss of consciousness from several minutes to hours, persistent headache or a headache that worsens with time, repeated vomiting or nausea, convulsions or seizures, dilation of one or both pupils of the eyes, and clear fluid draining from the nose or ears. We also may see an inability to awaken from sleep, loss of coordination, as well as weakness or numbness in fingers and toes. There are also cognitive or mental symptoms which include profound confusion and slurred speech. Agitation, combativeness or other unusual behavior has also been seen in those whom have suffered a moderate to severe TBI. In a severe injury, it is possible the patient may slip into a coma and other disorders of consciousness (The Mayo Clinic, 2014).

The role of age and/or gender in the outcome of a TBI

Does age play a role in the outcome of a TBI?

There is limited information on the impact of TBI on pediatric patients. There is growing concern regarding TBI's and the youth whom play contact sports. Past research has estimated a rate of at least a single TBI amongst high school athletes to be as high as "63% of a sample of 223 high school students" (Schatz, Moser, Covassin, & Karpf, 2011, p. 1563). And much like in "adults, high school and college athletes have been shown to increase their likelihood of sustaining a second concussion after the first" (Schatz, Moser, Covassin, & Karpf, 2011, p. 1563). Furthermore, "high school athletes who had sustained 3 or more concussions were more likely to experience loss of consciousness with future concussions" (Schatz, Moser, Covassin, &

Karpf, 2011, p. 1563). To add to this, otherwise "healthy high school students with a history of 2 or more concussions exhibited poorer performance on cognitive testing than healthy students with a history of 1 or no concussion" (Schatz, Moser, Covassin, & Karpf, 2011, p. 1563). There is significant evidence that "high school athletes with a history of 2 or more concussions endorsed higher ratings on headache, balance problems and dizziness…high school athletes with a history of 2 or more concussions endorsed higher ratings on nausea and fatigue" (Schatz, Moser, Covassin, & Karpf, 2011, p. 1564) when compared with athletes whom suffered one or no TBI's. Unfortunately Schatz, Moser, Covassin and Karpf's (2010) study was unable to draw a conclusion whether athletes were experiencing enduring postconcussion symptoms or rather, were more sensitive to physical, cognitive, and emotional fluctuations. It also is important to point out that the results of Schatz, Moser, Covassin, and Karpf's (2010) study were self-reported. Statistically, you stand a higher chance of bias in self-reported surveys because you are relying on the subject reporting their symptoms. Due to each person being different, it is possible that there may be inconsistency with the results. (Schatz, Moser, Covassin, & Karpf, 2011, p. 1566).

Meehan, Taylor and Proctor (2011) found that many student athletes do not seek emergency medical attention for a TBI. It is interesting to note that the "assessment and management of pediatric concussion is further complicated by the lack of injury reporting. In a 1983 study of football players in Minnesota high schools, 29% of athletes who sustained a concussion were not examined by anyone at all. Only 22% were examined by medical personnel. The remainder were attended to by a coach, parent, or teammate" (Meehan, Taylor, & Proctor, 2011, p. 3). One only needs to see this data to see how this can be a serious issue. This is a very important factor in regards to TBI care for young adults. It is important to realize that the

biomechanics of concussive injury differs between adult and pediatric patients" (Meehan, Taylor, & Proctor, 2011, p. 2). There is a difference in the "relative size of the head compared to the rest of the body, brain water content, vasculature, degree of myelination, and shape of the skull account for the biomechanical differences" (Meehan, Taylor, & Proctor, 2011, p. 2). TBIs are "caused primarily by a rotational acceleration of the brain" (Meehan, Taylor, & Proctor, 2011, p. 2). It also has been found that "as the neck muscles strengthen…this, in turn, reduces the resultant acceleration for a given force" (Meehan, Taylor, & Proctor, 2011, p. 2). There are two hypotheses in regards to this particular factor. Some believe the reduced muscle strength in the neck may put "younger athletes… at increased risk for concussion when hit with the same magnitude of force" (Meehan, Taylor, & Proctor, 2011, p. 2). Other researchers have hypothesized that the fact that younger athletes have less muscle strength in their neck may actually result in "less force delivered by the striking athlete at the time of injury, thereby decreasing the risk of injury" (Meehan, Taylor, & Proctor, 2011, p. 2). A counter to this hypothesis presented in Meehan, Taylor, and Proctor's (2011) study is the fact that "biomechanicians have demonstrated that greater force is required to cause similar concussive injury to smaller brains than in larger brains with greater mass" (Meehan, Taylor, & Proctor, 2011, p. 2). In other words, children showing symptoms of a TBI may have sustained a blow with greater force than an adult. The suggestion here is that the weaker neck muscles and larger head may play a more important role in sustaining a TBI than the overall smaller size of the athlete due to weaker forces being disproportionately applied to the brain (Meehan, Taylor, & Proctor, 2011, p. 2).

Meehan, Taylor and Proctor (2011) state that "pediatric and adult brains are in different phases of development, with the child's brain growing and needing to acquire high volumes of

new learning at a much faster pace. The pathophysiological response to TBI also differs between the mature and developing brain" (Meehan, Taylor, & Proctor, 2011, p. 2). Meehan, Taylor and Proctor (2011) state that children younger than three years of age were less likely to lose consciousness, where children three to nine years of age were more likely to lose consciousness, as well as were more prone to become comatose. Children three to nine years of age also experienced less subdural hemorrhages while having more significant cerebral edema. Children nine years and older who sustain a TBI display symptoms more in line with adults. Due to the "age dependent injury patterns" (Meehan, Taylor, & Proctor, 2011, p. 2) further investigation "into the possible differences in concussive brain injury between patients of varying ages" (Meehan, Taylor, & Proctor, 2011, p. 2) is warranted. For example, "diffuse brain swelling after TBI is more common in pediatric patients and results from mechanisms different from that of adults" (Meehan, Taylor, & Proctor, 2011, p. 3). Meehan, Taylor and Proctor state that the exact reason for this is unknown but it is suspected that differences in brain water content, dopaminergic activity, vascular response to injury, glutamate receptor expression, and expression of aquaporin 4 by microglia may play a role (Meehan, Taylor, & Proctor, 2011, p. 3).

Recovery time for a TBI can vary, but Meehan, Taylor and Proctor (2011) suggest that younger athletes require a longer recovery time, which may possibly be related to age-dependent brain physiology. The "underdeveloped or developing skills are presumed to be particularly vulnerable" (Meehan, Taylor, & Proctor, 2011, p. 6). It has been suggested that "early insult may have a significant impact on later development" (Meehan, Taylor, & Proctor, 2011, p. 6). There is "evidence that concussive injuries sustained early in life may have minimal effect on already established cognitive skills but may significantly delay the development of future skills" (Meehan, Taylor, & Proctor, 2011, p. 6). We can see how this would have much more serious

ramifications on a younger brain as opposed to an adult's brain (Meehan, Taylor, & Proctor, 2011).

Does gender play a role in the outcome of a TBI?

Groswasser, Cohen, and Keren (1998) conducted a study to determine what, if any, gender differences there may be in the outcome of severe TBI. Like many studies, they could not inflict a TBI on someone for ethical reasons, so they determined the severity of the concussion by looking at the duration of unconsciousness and matched this time frame up for both male and female subjects. The predicted outcome after participation in an in-patient rehabilitation program was determined by the subject's work capacity. This study was one of the first to take an in depth look at gender differences, largely due to the fact that previous TBI patients were primarily male, outnumbering female patients three to one. This made it difficult to obtain a large enough sample size of female subjects to provide a reliable statistical analysis. Even in this particular study, 262 subjects were male and 72 subjects were female, which follows the three to one ratio, but researchers were able to obtain enough data to show statistical significance in regards to gender differences (Groswasser, Cohen, & Keren, 1998, p. 805).

If we look at the results of this study, the numbers may be deceiving, but the percentage is significant. After a severe TBI, 47.2% of female subjects as opposed to only 30.2% of male subjects were able to return to their pre-trauma working level. This is the biggest difference in the results, although it also is the most important one because the goal should be to return to pre-trauma working levels. When we look at lower level functioning where subjects could still obtain gainful employment although working at a lower level then pre-trauma levels, 31.9% of female subjects ranked at a lower level as opposed to 43.1% of male subjects. Sheltered living (non-gainful work) and unemployable levels were obviously not optimum recovery working levels.

When comparing males to females in these two categories, 20.9% of females as opposed to 26.7 males were in sheltered living or unemployable post-trauma. These results suggest there may be a correlation between TBI recovery and gender differences. Groswasser, Cohen, and Keren (1998) note that at the time of discharge, biological factors play an important factor, while psychosocial factors influence late outcomes. Groswasser, Cohen, and Keren (1998) also note that there is a difference between the organization of brain functions between females and males and this may also play a role in the outcome after a TBI, although this is unlikely due to the type of injury. All subjects suffered blunt head trauma that lead to diffuse axonal injury. The researchers did not do a detailed study of the focal lesions, but do to the large number of subjects in this study, it is unlikely that this factor has played a role in the outcome (Groswasser, Cohen, & Keren, 1998, p. 805-806).

What has been hypothesized in this study, and has been supported in other studies is well, is the role progesterone in females plays in the recovery of TBI. Stein, Wright and Kellermann (2008) conducted a literature review examining the possible neuroprotective properties of progesterone, which would support the previous study by Groswasser, Cohen and Keren. To think that progesterone has properties that may help someone recover from a TBI is not illogical. Researchers have found that "administering relatively large doses of progesterone during the first few hours to days after an injury significantly limits central nervous system (CNS) damage, reduces loss of neural tissue, and improves functional recovery" (Stein, Wright, & Kellermann, 2008), p. 164). While our focus for the purpose of this paper is on TBI, it is important to note that progesterone has been shown to possibly protect "from several forms of acute CNS injury, including penetrating brain trauma, stroke, anoxic brain injury, and spinal cord injury (Stein, Wright, & Kellermann, 2008, p. 164). Stein, Wright, and Kellermann (2008) hypothesize that

progesterone protects or rebuilds the blood-brain barrier, which in turn decreases the development of cerebral edema, reducing inflammation, and it also may limit cellular necrosis and apoptosis (Stein, Wright, & Kellermann, 2008, p. 164).

The researchers of this article summarize the cascading effect of brain trauma quite well by stating that the tissue damage and destruction that accompanies the initial trauma put in motion a deleterious process within the brain that can progressively enlarge the injured area, leading to a lifetime of disability or even death. Changes, some of which are "pathosphysiologic changes include release of excitatory amino acids, activation of the *N*-methyl-D-aspartate receptor, the influx of toxic levels of calcium into neurons, activation of proinflammatory cytokines, and other events" (Stein, Wright, & Kellermann, 2008, p. 164). Progesterone may possibly block one or more of these cascading effects, therefore limiting or even preventing further damage due to TBI. Previously there were only five treatments for TBI, which included "hyperventilation, mannitol, cerebrospinal fluid drainage, barbiturates, and corticosteroids" (Stein, Wright, & Kellermann, 2008, p. 165). None of these treatments helped as we did not see a "decrease in morbidity or mortality after traumatic brain injury" (Stein, Wright, & Kellermann, 2008, p. 165). This is why promising results of progesterone are so important. The study does note, that while not an optimum treatment for older patients, hypothermia has shown promising results in some TBI subjects (Stein, Wright, & Kellermann, 2008). This as well is not unheard of as we have seen promising results of hypothermia in spinal cord injury subjects (Dimar et al., 2000).

Progesterone treatment has shown promise in both females and males while conducting studies with rats. Stein, Wright, and Kellermann (2008) tested a control group of male and female rats that were treated with peanut oil vehicle after injury, while another group of male and

female rats were treated with progesterone after injury. When the brains of the subject rats were examined 72 hours later, rats whom were treated with progesterone showed significantly less cerebral edema than those rats treated with peanut oil vehicle. While limiting further injury is important, the main goal after a TBI should be to improve function of the subject after injury. Stein's team studied four different categories of rats while conducting a Morris water maze, which is a spatial navigation task. The groups of rats included head-trauma rats treated with progesterone, head-trauma rats treated with a placebo, uninjured sham surgery controls with a placebo, and uninjured sham surgery controls treated with progesterone. Several days later these rats were tested in the Morris water maze, and it was found that the head-trauma rats treated with progesterone performed the task significantly faster than placebo treated controls and nearly as well as the sham surgery group (Stein, Wright, & Kellermann, 2008, p. 165-166).

A possible reason for these promising results in tests with progesterone, besides the reduction of cerebral edema, is the "reduction of glutamate toxicity by decreasing the expression and by up-regulating GABA" (Stein, Wright, & Kellermann, 2008, p. 166). Stein, Wright, and Kellermann state that "GABA-mediated inhibition can decrease excessive injury-induced excitotoxicity caused by the release of glutamate or other excitatory neurotransmitters" (Stein, Wright, & Kellermann, 2008, p. 168). This is the opposite of corticosteroid treatment which has been used in the past as "methylprednisolone treatment is deleterious in the setting of traumatic brain injury" (Stein, Wright, & Kellermann, 2008, p. 166). The studies that show both male and female rats benefit from progesterone after head trauma suggests that gender is not as much of a factor as the hormone progesterone (Stein, Wright, & Kellermann, 2008).

While progesterone sounds like a miracle treatment for TBI's, not everything is positive. Stein, Wright and Kellermann cited the Women's Health Initiative study. This study found that

long-term hormonal replacement therapies such as estrogen and Provera (a synthetic "progesterone-like" molecule) can increase a woman's risk of stroke and heart disease. This suggests looking at a risk analysis when considering progesterone treatment as a neuroprotectant. The study does note that Provera administered with estrogen is a procoagulant. Secondly, subjects in the Women's Health Initiative study took both hormones over an extended period of time, not short term, which would generally be the case when used to treat a TBI as a neuroprotectant. Furthermore, Provera, or medroxyprogesterone acetate (MPA) "exhibits different molecular and clinical properties from natural progesterone" (Stein, Wright, & Kellermann, 2008, p. 169). Provera is a synthetic progestin, and "synthetic progestins in general have different clinical properties and may not all be neuroprotective" (Stein, Wright, & Kellermann, 2008, p. 169). Stein and his team found that while MPA does reduce cerebral swelling after a TBI, it does not improve the functional outcome. Stein, Wright, and Kellermann stated that MPA blocked estrogen-induced neuroprotection, as well as enhanced calcium toxicity and failed to produce any beneficial effects (Stein, Wright, & Kellermann, 2008, p. 169).

The research on progesterone and the neuroprotective properties it has shown to possess is so important because it has shown promise in rats, as well as the single human trial conducted as of the date of Stein, Wright and Kellerman's study (Stein, Wright, & Kellermann, 2008, p. 169). In the human trial conducted by Wright, Ritchie, Mullins, Kellermann, and Denson (2005), the subjects received progesterone via continuous infusion intravenously. Control subjects received a placebo. This study suggests the treatment is safe and there were no major differences in regards to gender (Wright, Ritchie, Mullins, Kellermann, & Denson, 2005). While the results were promising in this single human study, the sample pool was rather small with only 100

subjects. This human trial does suggest that further investigation is warranted and should be investigated (Stein, Wright, & Kellermann, 2008).

Do genetics play a role in recovery from a TBI?

We have explored age and gender, but do genetics play a role in TBI's? Dardiotis et al. (2010) found mounting evidence that suggests various genetic elements in the pathophysiology of brain trauma. Dardiotis et al. (2010) goes on to suggest that the extent of brain injury after the TBI may be modulated to some extent by genetic variants. Dardiotis' study focuses on both primary and secondary effects of TBI which is important because it is suggested that several genes are factors in the pathophysiology of secondary brain damage. It is these secondary processes that have been found to dramatically worsen the primary damage, which lead to a cascade of axonal and neuronal pathologies. These cascading effects can determine the subject's overall clinical outcome after a TBI. Following the initial brain changes, we also will see cellular, neurochemical, and molecular changes due to the TBI. These changes may include "neuronal cell death, apoptosis, excitotoxicity, inflammatory infiltration, Aβ-peptide (Aβ) deposition, disruption of calcium homeostasis, oxidative stress, and cytoskeletal and mitochondrial sysfunction" (Dardiotis et al., 2010, p. 1). The deposition of Aβ is important because of its role in diffuse plaques seen in the brains of those whom have suffered multiple TBI's and develop neurodegenerative diseases, including Alzheimer's disease (AD) when examining the brains of subjects post mortem (Lendon et al., 2003, p. 685).

The Apolipoprotein E (ApoE) is a "plasma lipoprotein implicated mainly in transporting cholesterol and lipids throughout the tissues including the CNS" (Dardiotis et al., 2010, p. 2). ApoE in the brain is "synthesized primarily by the astrocytes and the microglia plays a vital role in maintenance of neuronal membranes, neuronal tissue repair, remodeling, and synaptogenesis"

(Dardiotis et al., 2010, p. 2). It has been suggested that the ApoE4 allele, present after a TBI, may increase the risk of a poor clinical outcome after the injury (Dardiotis et al., 2010, p. 2-6). The ApoE4 allele is important because it is a risk factor for developing AD as well as a poorer outcome after a TBI. After an acute TBI, we see a striking increase of intraneuronal ApoE. Due to ApoE's role in neural injury and repair, it is reasonable to think the increased levels of ApoE after a TBI could affect long term recovery after the injury. As we will see later, there are strong ties between those whom suffer multiple TBI's, along with the presence of ApoE, and Aβ and the relation to AD (Lendon et al., 2003, p. 683). Genetics plays a role in neurodegenerative diseases as well, as do other factors such as TBI.

Neurodegenerative Disease

To understand what a neurodegenerative disease is, we must look at what a neuron is first. JPND (Joint Programme – Neurodegenerative Disease) Research states "neurons are the building blocks of the nervous system which includes the brain and spinal cord. Neurons normally don't reproduce or replace themselves, so when they become damaged or die they cannot be replaced by the body" (JPND Research, 2015). Because "neurodegenerative disease is an umbrella term for a range of conditions which primarily affect the neurons in the human brain" (JPND Research, 2015) there is no one conclusive definition of what neurodegenerative disease actually is. The Ontario Brain Institute published an information pamphlet on neurodegeneration recently that described neurodegeneration as the "gradual deterioration in a person's cognitive abilities, such as memory. This loss is due to either structural changes that prevent neurons (brain cells) from functioning normally, or to cell death. Neurodegeneration is a key feature of several diseases that are referred to as "neurodegenerative diseases" (Ontario Brain Institute, 2015). Some of these diseases or disorders include Multiple Sclerosis (MS),

Myasthenia Gravis, Amyotrophic Lateral Sclerosis (ALS or Lou Gehrigs Disease), Alzhiemer's Disease (AD), Dementia, and cognitive disorders (Henry Ford Health System – Neuroscience Institute), motor neuron diseases (MND), Parkinson's Disease (PD) and PD-related disorders, Huntington's Disease (HD) (JPND Research, 2015) and Chronic Traumatic Encephalopathy (CTE). For the purpose of this study I will focus on ALS, PD, AD and related dementia, and CTE.

Amyotrophic Lateral Sclerosis (AS)

ALS is "an idiopathic, fatal neurodegenerative disease of the human motor system" (Kiernan et al., 2011, p. 942). The New England Journal of Medicine states that "'Amyotrophic' refers to the muscle atrophy, weakness, and fascination that signify disease of the lower motor neurons. 'Lateral sclerosis' refers to the hardness to palpation of the lateral columns of the spinal cord in autopsy specimens, where gliosis follows degeneration of the corticospinal tracts" (Rowland & Shneider, 2001, p. 1688). While there have been different hypotheses on the cause of ALS proposed over the years, ALS "remains poorly understood in terms of a unifying causal hypothesis and indeed, might turn out to be a common end-stage phenotype of diverse causes" (Mitchell & Borasio, 2007, p. 2033). Some of these proposed hypotheses for the cause of ALS include occupational and environmental exposures, heavy-metal toxic effects, oxidant stress, toxic stress and excitotoxicity (Mitchell & Borasio, 2007, p.2033). Currently, one of the focuses of ALS research is excitotoxicity, which is "the process by which amino acid neuromodulators such as glutamate become toxic when present at supraphysiological concentrations. Other potential excitotoxins include AMPA and kainite" (Mitchell & Borasio, 2007, p. 2033). Still other hypotheses have focused on protein aggregation, dysregulation of intracellular calcium, and axonal transport defects (Mitchell & Borasio, 2007, p. 2034).

Diagnosing ALS focuses on both upper and lower neuron degeneration with a set criteria that needs to be met before a clinical diagnosis can be made.

"The diagnosis of ALS requires:

(A) the presence of:

(A:1) evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiological or neuropathologic evaluation.

(A:2) evidence of upper motor neuron (UMN) degeneration by clinical examination, and

(A:3) progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination,

together with:

(B) the absence of

(B:1) electrophysiological or pathological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration, and

(B:2) neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs" (Brooks, Miller, Swash, & Munsat, 2000, p. 293).

Upon examination, a careful, thorough history as well as physical and neurological examination "must search for clinical evidence of UMN and LMN signs in four regions (brainstem, cervical, thoracic, or lumbosacral spinal cord) of the central nervous system (CNS)" (Brooks et al., 2000, p. 293-294). There also are important features that, while present with other neurodegenerative

diseases, will help to rule out a diagnosis of ALS or suggest the presence of another disease. These include "plaques of multiple sclerosis and a focal cause of myelopathy" (Brooks et al., 2000, p. 299).

Parkinson's Disease (PD)

PD is another neurodegenerative disease that the Mayo Clinic describes as

> "a progressive disorder of the nervous system that affects your movement. It develops gradually, sometimes starting with a barely noticeable tremor in just one hand. But while a tremor may be the most well-known sign of Parkinson's disease, the disorder also commonly causes stiffness or slowing of movement. In the early stages of Parkinson's disease, your face may show little or no expression or your arms may not swing when you walk. Your speech may become soft or slurred. Parkinson's disease symptoms worsen as your condition progresses over time" (www.mayoclinic.org, 2014).

While PD is the most widespread neurodegenerative movement disorder that we see in the aging of the human nervous system, a conclusive diagnosis requires post mortem verification (Tredici, Rub, De Vos, Bohl, & Braak, 2002, p. 413).

Much like we may see in AD, in PD we see "susceptible regions and vulnerable nerve cell populations become progressively impaired owing to the extensive presence of Lewy neurites and Lewy bodies" (Tredici et al., 2002, p. 413). Presently, there is no therapy that has been proven to be neuroprotective or neurorestorative (Gupta, Dawson, & Dawson, 2008, p. 1), but we do have promising leads when we search for causes of PD. Gupta, Dawson, and Dawson state that "human postmortem material, animal models, and genetic analyses have provided important clues to the etiology of PD. In particular, the genetic approach has recently unraveled a

series of proteins that when mutated can cause familial forms of PD…this approach provides an entry into identifying the signaling pathways that go errant during the development of PD. Understanding these signaling pathways to neurodegeneration in PD will undoubtedly allow for important access points for drug targeting" (Gupta, Dawson, & Dawson, 2008, p. 1-2). Another possible cause of PD may be illegal drug use, and in particular those drugs that impact the dopamine receptors in the brain. Cocaine is known as a drug that impacts the pleasure pathways of the brain, or the dopamine receptors. We see dopamine replacement therapy (DRT), and the dependence on DRT in many cases of PD. For example, in a study by Bearn, Evans, Kelleher, Turner, and Lees, they note that "DRT is an established treatment for patients with PD" (Bearn, Evans, Kelleher, Turner, & Lees, 2004, p.305). Giovannoni, O'Sullivan, Turner, Manson, and Lees (2000) concur with this as they state "hedonistic homeostatic dysregulation is a neuropsychological behavioral disorder associated with substance misuse and addiction. The disorder has been recognized as a consequence of DRT in 15 patients with Parkinson's disease" (Giovannoni, O'Sullivan, Turner, Manson, & Lees, 2000, p. 423). The conclusion between cocaine use and DRT is made by Bearn et al. (2004) where they found that "done-dependent adverse effects of DRT include chorea and dystonia, mood swings and psychosis. Cocaine induces motor stereotypies and reversible chorea through its effects on dorsal basal ganglia dopaminergic systems. Depression, mood swings, paranoia, panic attacks and psychosis are common complications of habitual cocaine use. Thus, both the clinical and neurochemical effects of cocaine and amphetamine on dopaminergic neurotransmission are similar to those of DRT" (Bearn et al., 2004, p. 306). This fact is made even clearer when one considers that "it is hypothesized that chronic DRT may be complicated by a maladaptive pattern of dependent use in

some patients with PD, the symptoms of which are analogous to those of cocaine dependence" (Bearn et al., 2004, p. 306).

Alzheimer's Disease (AD)

AD and related dementia are caused by "plaques… deposits of a protein fragment called beta-amyloid (Aβ) that build up in the spaces between nerve cells. Tangles are twisted fibers of another protein called tau that build up inside cells" (Alzheimer's Association, 2015, p. 210). Also present in the brains of patients with AD is "progressive dementia accompanied by neural cell loss. The findings that mutations in the tau gene are responsible for frontal temporal dementia proved that formation of neurofibrillary tangles has neurotoxic consequences" (Rogaeva, 2002, p. 1). According to the Mayo Clinic, some symptoms of AD are

> "troubles with memory, disorientation and misinterpretation of spatial relationships, speaking and writing, thinking and reasoning, making judgments and decisions, planning and performing familiar tasks, changes in personality and behavior which include depression, anxiety, social withdrawal, mood swings, distrust in others, irritability and aggressiveness, changes in sleeping habits, wandering, loss of inhibitions, and delusions" (Mayo Clinic, 2014).

It is also important to consider that AD can be early onset in some cases. Rogaeva suggests that early onset AD is genetic, linking the disease to "βAPP gene located on chromosome 21… AD-associated mutation in the βapp gene are clustered near the α-, β-, or γ-secretase cleavage sites, demonstrating that they have a direct effect on βAPP processing" (Rogaeva, 2002, p. 2). Head trauma in early adult life has been suspected to be associated with increased risk of AD and dementia in late life. Plassman et al. (2000) found this to be true, as well as the more severe the

injury, the greater the risk of developing AD and dementia later in life (Plassman et. al, 2000, p. 1163). This association remains the same for early onset AD, as "evidence from animal and human experiments demonstrate links between TBI and the subsequent onset of premature, psychiatric syndromes and neurodegenerative diseases, including AD and PD" (Kiraly & Kiraly, 2007, p. 1768).

Chronic Traumatic Encephalopathy (CTE)

Chronic Traumatic Encephalopathy, or CTE, was discovered by Dr. Bennett Omalu when examining the brains of football players, in particular Mike Webster, in 2002 (Benet et. al, 2011, p. 1). Dr. Omalu, as well as other researchers and the Brain Injury Research Institute, have described and identified CTE in numerous contact sports athletes including football players, boxers, professional wrestlers, and ice hockey players (Bennet et. al, 2011, p. 1). Gavett, Stern, and McKee (2011) describe CTE as "a form of neurodegeneration that is believed to result from repeated head injuries. Originally termed *dementia pugilistica* due to its association with boxing… CTE has recently been found to occur following other causes of repeated head trauma, suggesting that any repeated blows to the head, such as those that occur due to American football, hockey, soccer, professional wrestling, and physical abuse, can also lead to neurodegenerative changes" (Gavett, Stern & McKee, 2011, p. 1). Key amongst the pathological changes in the brain are changes in cerebral atrophy, dense tau immunoreactive inclusions (neurpfibrillary tangles, glial tangles, and neuropil neutrites), and diffuse axonal injury (Gavett, Stern, & McKee, 2011, p. 1). There are also psychological changes which include "disordered memory and executive functioning, behavioral and personality disturbances (e.g., apathy, depression, irritability, impulsiveness, suicidality), parkinsonism, and occasionally, motor neuron

disease. At the present time, there are no formal clinical or pathological diagnostic criteria for CTE" (Gavett, Stern & McKee, 2011, p.1).

While CTE is associated with repeated concussions, "CTE is a neurodegenerative disease that occurs years or decades following recovery from the acute or post-acute effects of head trauma. The onset of CTE is often mid-life, usually after the athlete has retired from her or her sport" (Gavett, Stern, & McKee, 2011, p. 2). Some of the earliest symptoms of CTE are behavioral; "in particular, individuals with neuopathologically-documented CTE have been described by family and friends as being more irritable, angry, apathetic, or having a shorter fuse. Increased suicidality appears to be a particularly salient symptom caused by CTE" (Gavett, Stern & McKee, 2011, p. 2). Cognitive abilities can also be affected by CTE, with some of the first symptoms including poor executive functioning as well as diminished episodic memory (Gavett, Stern, & McKee, 2011, p. 2). As the disease progresses, "movement (e.g., parkinsonism), speech, and ocular abnormalities may emerge in the context of declining cognition and worsening comportment. A minority of cases with neuropathologically-documented CTE developed dementia before death; the relative infrequency of dementia in individuals with CTE may be due in part to the fact that many individuals with CTE have either committed suicide or died from accidents or drug overdose at an early age" (Gavett, Stern, McKee, 2011, p. 3).

The correlation between TBI and neurodegenerative disease

There has been a link between TBI's (both mTBI and TBI) in the past and neurodegenerative diseases which I will show as we progress further. Some of these links are controversial such as the case of PD, while others we see a definitive correlation such as in those

afflicted with CTE. I will look at three neurodegenerative disorders in particular, those being PD, AD, and CTE.

Parkinson's Disease

While there has been much "interest in the potential relationship between TBI and subsequent development of idiopathic PD, results from epidemiological studies have thus far been mixed. In support of this proposed relationship, parkinsonism syndrome has been observed after TBI, or as part of the clinical presentation of CTE" (Wong & Hazrati, 2013, p. 103). Even though the "pathology of PD is well recognized, the mechanisms of neuronal death are uncertain. Experimental studies have implicated oxygen free radicals and oxidative stress. α-Syn, which is implicated in other neurodegenerative diseases such as AD, may play a role in development of PD after TBI" (Masel & DeWitt, 2010, p. 1533). The key here may be α-Syn immunoreactivity, as it is considered an important pathological finding in Lewy body dementia, multi-system atrophy, and PD. When examining brain tissue samples from TBI patients, Masel and DeWitt (2010) observed increased levels of α-syn (Masel & DeWitt, 2010, p. 1533).

Goldman et. al, (2006) found results that suggest "mild-to-moderate closed head injury may increase PD risk decades later" (Goldman et. al, 2006, p. 65). Because previous studies have shown to be inconsistent and the link between TBI and PD remains controversial, Goldman et. al (2006) tried to limit independent variables that may affect the results of their study (Goldman et. al, 2006, p. 65-67). The study does this by "testing the hypothesis that head injury increases PD risk in twins discordant for PD. Twins are genetically identical or similar, which thereby controls for the potential confounding effects of genetic factors. Also, twins' environments are much more similar than those of typical cases and control subjects, which thereby controls for many confounding environmental factor, both recognized and unrecognized" (Goldman et. al, 2006, p.

65). Goldman et. al, (2006) did find that, much like other neurodegenerative diseases, the more TBI's suffered by a patient, the higher the risk was for developing PD (Goldman et. al, 2006, p. 67).

Alzheimer's Disease

We have seen a definitive link between AD and TBI's, in particular early onset AD and repetitive TBI's. Sivanandam and Thakur's (2012) study states that a TBI initiates a disease process. To expand on this hypothesis, the study explains that "although many patients survive the initial insult (injury), TBI initiates a chronic disease process that may ultimately contribute to their deaths months to years later. Cell death after TBI is a major cause of neurological deficits and mortality. TBI is a disease process with an initial injury that induces biochemical and cellular changes which in turn contribute to continuing neuronal damage and death over time. This continuing damage is known as secondary injury, and as a part of this process, multiple apoptotic and inflammatory pathways are activated. The state of cerebral environment and resultant secondary responses to TBI ultimately determine the final outcome" (Sivanandam & Thakur, 2012, p. 1377). As stated previously, AD is caused by the buildup of Aβ proteins in the brain. Sivanandam and Thakur (2012) point out that there are

> "many pathological features common to both acute brain injury and AD, including Aβ deposition, tau phosphorylation, neurite degeneration, synapse loss and microgliosis. Neuroinflammatory responses may serve as a common denominator between these two entities, and play a central role in mediating secondary neuronal injury in both chronic neurodegenerative diseases and acute brain injury…. Although TBI is associated with AD, the role played by TBI in the mechanism of disease development and progression is not clearly understood. Primary feature of TBI is axonal damage and it is clear from

> many studies that axonal defect is a key disease manifestation of AD and responsible for its symptoms" (Sivanandam & Thakur, 2012, p. 1377).

Furthermore, when looking at Aβ deposition and tau phosphorylation, we discover the "Amyloid Cascade Hypothesis" suggested by Heuvel, Thornton, and Vink (2007). From a neuropathological stance,

> "AD is characterized by the presence of neurofibrillary tangles (NFTs) and neuritic plaques. NFTs in the brain consist primarily of hyperphosphorylated tau. Neuritic amyloid plaques consist primarily of aggregated amyloid-β peptides (Aβ), a peptide of 40-42 amino acids, which are surrounded by dystrophic neurites, microglia and retroactive astrocytes. It is now generally accepted that the development of these two pathologies is central to the pathogenesis of AD and the leading 'amyloid cascade hypothesis' suggests that it is the accumulation of Aβ in the brain which is the primary influence in AD. Aβ has been hypothesized to cause the pathologic and behavioral manifestations of AD, including neurofibrillary tangle formation, neuronal degeneration, synaptic dysfunction and loss as well as impaired memory. According to this theory, the accompanying NFT formation and neuronal loss are downstream events resulting from an imbalance between Aβ production from its precursor Amyloid Precursor Protein (APP)" (Van Den Heuvel, Thornton, & Vink, 2007, p. 304).

A relationship has been suggested between "TBI and AD since TBI leads to overexpression of APP within neuronal cell bodies and accumulation of APP within traumatically injured axons. Theoretically, the accumulation of APP results in an increase in the substrate that could potentially be processed to form amyloidogenic Aβ. It has therefore been hypothesized by a number of groups that the overexpression of APP may exceed the limit of normal processing

capacity, resulting in mismetabolization of APP into potentially amyloidogenic fragments" (Van Den Heuval, Thornton, & Vink, 2007, p. 306).

The evidence of a correlation between TBI and early onset AD is due to a case report documenting a 38-year old man who previously suffered a single severe TBI. Since then, numerous studies of the brains of boxers suffering from CTE (dementia pugilistica) have also demonstrated AD-like pathology with diffuse Aβ plaque deposition. It is fair to speculate that such Aβ deposition resulted from repeated blows to the head over a long period of time. It also is fair to speculate that such events may also occur in the brains of others whom have suffered repetitive head trauma (Van Den Heuval, Thornton, & Vink, 2007, p. 307). Van Den Heuval, Thornton, and Vink (2007) state that "histopathological studies of such individuals who died after suffering a single severe TBI demonstrate widespread cerebral Aβ deposition in short and long term survivors irrespective of age" (Van Den Heuval, Thornton, & Vink, 2007, p. 307). Van Den Heuval, Thornton, & Vink (2007) do make note that there are discrepancies in these findings as in other studies very few, and in some instances, no subjects showed any evidence of Aβ plaques.

Chronic Traumatic Encephalopathy

Where we have seen suggestions of a correlation between neurodegenerative disease and TBIs, when we look at CTE there is a wealth of evidence that supports this correlation. Omalu, Hamilton, Kamboh, DeKosky, and Bailes (2010) state that "CTE represents the cumulative, long term neurologic consequences of repetitive concussive and subconcussive blows to the brain" (Omalu, Hamilton, Kamboh, DeKosky, & Bailes, 2010, p. 40). It is important to note that, possibly because CTE is a relatively new disease discovered in 2002 by Dr. Bennett Omalu, risk factors for CTE other than repetitive brain trauma may exist and are unknown at this time

(Baugh et al., 2012, p. 244). McKee et al. (2013) mention four symptomatic stages in regards to CTE. The symptoms of "stage I CTE include headache and loss of attention and concentration. Additional symptoms in stage II included depression, explosivity, and short term memory loss. In stage III, executive dysfunction and cognitive impairment were found, and in stage IV, dementia, word finding difficulty and aggression were characteristic" (McKee et al., 2013, p. 43-44). These symptoms typically do not present themselves until "8-10 years after experiencing repetitive mild traumatic brain injury" (McKee et al., 2013, p. 44). This study also notes that "there is an ordered and predictable progression of hyperphosphorylated tau abnormalities through the nervous system in CTE that occurs in conjunction with widespread axonal disruption and loss. The frequent association of CTE with other neurodegenerative disorders suggests that repetitive brain trauma and hyperphosphorylated tau protein deposition promote the accumulation of other abnormally aggregated proteins including TAR DNA-binding protein 43, amyloid beta protein and alpha-synuclein" (McKee et al., 2013, p. 44). There are some similarities between AD and CTE, and to help distinguish between the two, I included Table 1 which was published in McKee et al., (2013).

Current and future advances in treating TBIs and neurodegenerative disease

While we have medications and certain psychotherapy techniques to relieve some symptoms of the effects of TBI and neurodegenerative disease, in particular depression, anxiety and headaches, the scientific community is searching for possible ways to cure or stop the progression of neurodegenerative disease. As seen below, progress is being made but we are not quite to the point we need to be yet.

It seems that as a society we feel there is or should be a drug for everything. Unfortunately with neurodegenerative diseases, that is not always the case. Modi, Pillay, and

Choonara (2010) stated that "due to limitations posed by the restrictive blood-brain barrier (BBB), conventional drug delivery systems do not provide adequate cyto-architecture restoration and connection patterns that are essential for functional recovery in neurodegenerative disorders(NDs)" (Modi, Pillay, & Choonara, 2010, p. 154). This is the reason why I will focus less on pharmaceutical options and place more emphasis on alternative treatments.

Nanotechnology

A recent advancement in treating neurodegenerative disease utilizes nanoparticles. Due to their small size, "nanotechnology employs engineered materials or devices that interact with biological systems at a molecular level and could revolutionize the treatment of NDs by stimulating, responding to, and interacting with target sides to induce physiological responses while minimizing side effects" (Modi, Pillay, & Choonara, 2010, p. 154). Fernandes, Soni, and Patravale (2010) concur with this hypothesis. The blood brain barrier is unique in that "unlike peripheral capillaries that allow relatively free exchange of substances across/between blood and tissue parenchyma, the BBB strictly limits transport into the brain through both physical (tight junctions) and metabolic (enzymes) barriers" (Fernandes, Soni, & Patravale, 2010, p. 167). Lipid-based nanoparticles and polymeric nanoparticles are the two existing nanoparticulate system categories (Fernandes, Soni,& Patravale, 2010, p. 173). It also is important to note that the "lack of toxicology data on nanocarrier systems hinders governmental regulation. Currently, no regulatory requirement to test nanoparticles for health, safety, and environmental impacts has been formalized. Toxicity studies are critical to establish the full in vivo potential of nanotechnology and nanomedicine in particular. Understanding the physiochemical, molecular, and physiological processes of nanoparticles is imperative for nanomedicine to become a reliable and sustainable treatment modality" (Fernandes, Soni, & Patravale, 2010, p. 175).

Medical Marijuana (CBDs)

Although controversial, marijuana has proven beneficial in the treatment of neurodegenerative diseases. The focus of the medicinal use of marijuana is on cannabidiol (CBD), which lacks any psychotropic effect usually associated with marijuana (Iuvone, Esposito, De Filippis, Scuderi, & Steardo, 2009, p. 65). There are three different groups of cannabinoids (CDs), with CBD being extracted from phytocannabinoids (Iuvone, Esposito, De Filippis, Scuderi, & Steardo, 2009, p. 66). There are "two membrane receptors for CBs, both coupled to G_1 protein, and named CB_1 and CB_2 have been identified so far. … it has been reported that CB_1 agonism was able to prevent tau hyperphosphorylation in cultured neurons and antagonize cellular changes and behavioral consequences in β-anyloid-induced rodents" (Iuvone, Esposito, De Filippis, Scuderi, & Steardo, 2009, p. 66). Both CB_1 and CB_2 protective roles have "been recognized not only in AD models but also in other experimental paradigms of neurodegenerative disorders" (Iuvone, Esposito, De Filippis, Scuderi, & Steardo, 2009, p. 67). There is "growing evidence that CB_1, and possibly CB_2, receptor interactions could affect neuropathology and disease progression in rodent model of both MS and ALS" (Iuvone, Esposito, De Filippis, Scuderi, & Steardo, 2009, p. 67). CBD has been shown to have therapeutic properties in experiments in regards to anxiolytic, anticonvulsant, anti-oxidant, anti-emetic, anti-inflammatory, and antipsychotic agent. This makes CBDs a potential medicine for the treatment of oxidative injury, epilepsy, neuroinflammation, anxiety, schizophrenia, vomiting, and nausea (Fernàndez-Rulz et al., 2012, p. 1). Due to CBDs anti-inflammatory and anti-oxidant properties, "the neuroprotective potential of CBD is of particular interest and is presently under intense

preclinical research in numerous neurodegenerative disorders" (Fernàndez-Rulz et al., 2012, p. 1).

While only three years apart, it is important to note a key difference between these studies. While Iuvone, Esposito, De Filippis, Scuderi, and Steardo (2009) place emphasis on CB_1, Fernàndez-Rulz et al., (2012) instead states that CB_1 is not activated. So as we can see, therapeutic use of CBD is an evolving field. This could be in part due to research into endocannabinoids, which "differ in chemical structure from phytocannabinoids. Among the endocannabinoids so far identified are anandamide (N-arachidonoylethanolamide, AEA), 2-arachidonoylglycerol (2-AG), 2-arachidonoylglycerol ether (noladin ether), O-arachidonoyl-ethanolamine (virodhamine), and N-arachidonoyl-dopamine (NADA). The first two discovered endocannabinoids, anandamide and 2-AG, have been most studied" (Grotenhermen, 2006, p. 3). Tanveer, McGuinness, Daniel, Gowran, and Campbell (2012) created a flow chart (Figure 2) that shows a good representation of how CBDs can have medicinal benefits to those suffering from neurodegenerative disease. Because AD is a neurodegenerative disease that has an inflammatory component, "the endocannabinoid system has attracted interest as a novel target for AD, as well as other neurodegenerative disorders, due to the potential neuroprotective, anti-inflammatory, and neurotrophic properties of cannabinoid compounds" (Tanveer, McGuinness, Daniel, Gowran & Campbell, 2012, p. 633-634). Due to psychological effects of neurodegenerative diseases, it is important to note that use of CBDs may reduce anxiety as well as can be used as an antipsychotic agent as stated above. Tanveer, McGuinness, Daniel, Gowran, and Campbell (2012) also note that cannabinoid-based medications may assist in the treatment and management of behavioral symptoms of some neurodegenerative diseases (Tanveer, McGuinness, Daniel, Gowran, & Campbell, 2012, p. 634).

Stem Cell Treatment

Yet another controversial method for treating neurodegenerative disease might be stem cell treatments. Lindvall, Kokaia, and Martinez-Serrano (2004) state that "recent progress shows that neurons suitable for transplantation can be generated from stem cells in culture, and that the adult brain produces new neurons from its own stem cells in response to injury" (Lindvall, Kokaia, & Martinez-Serranao, 2004, p. S42). While studying animals, it was "demonstrated that neuronal replacement and partial reconstruction of damaged neuronal circuitry is possible. There is also evidence from clinical trials that cell replacement in the diseased human brain can lead to symptomatic relief "(Lindvall, Kokaia, & Martiniez-Serrano, 2004, p. S42). It is important to recognize that in each neurodegenerative disease, "a different spectrum of cell types is affected; therefore, different types of neurons are required for replacement" (Lindvall, Kokaia, & Martiniez-Serrano, 2004, p.S42). Thus far, "the research has advanced furthest in diseases of the basal ganglia, namely Parkinson's disease, and Huntington's disease, and of these two conditions the development of stem cells as a donor source has advanced furthest for Parkinson's disease. However, a variety of other neurodegeneration conditions, including ALS, Alzheimer's disease, and demyelinating diseases such as MS are potential targets for circuit repair" (Rosser, Zietlow, & Dunnett, 2007, p. 689). In order for stem cells to repair neuronal circuits, "donor cells must be able to integrate into the damaged host tissue and make synapses with host neurons. A major requirement in achieving circuit repair is to persuade potential donor cells to adopt the precise neural phenotype of the cells lost to the disease process… there is a considerable body of work that demonstrate that this is an absolute requirement for recovery of function" (Rosser, Zietlow, & Dunnett, 2007, p. 689).

Ultrasound Treatment

As mentioned previously, one of the largest hurdles to treatment of neurodegenerative diseases has been the blood brain barrier and the protective properties of this barrier. Furthermore, a key component in neurodegenerative disease is amyloid-β proteins, tau protiens, and neurofibrillary tangles. Jordão et al., (2013) utilized a noninvasive technique that "targeted drug delivery to the brain… using transcranial focused ultrasound (FUS), which transiently increases permeability of the blood-brain barrier (BBB) for localized delivery of therapeutics from the blood to the brain" (Jordão et al., 2013, p. 1). In addition to permeating the BBB, Jordão et al., (2013) also found that "FUS can deliver intravenously-administered antibodies to the brain of a mouse model of AD and rapidly reduce plaques composed of amyloid-β peptides (Aβ). … We demonstrate that transcranial FUS application leads to a significant reduction in plaque burden four days after a single treatment in the TgCRND8 mouse model of AD and that endogenous antibodies are found bound to Aβ plaques" (Jordão et al., 2013, p. 1). This is important due to the role that plaques play in neurodegenerative diseases.

The importance of amyloid-β plaques cannot be understated, and a non-pharmacological approach to reducing these plaques could prove very beneficial to those suffering from neurodegenerative disease in the future. Recently it was found that ultrasound may show promise in reducing the Aβ and possibly restore memory in those affected by AD. Leinenga and Götz (2015) presented a "non-pharmacological approach for removing Aβ and restoring memory function in a mouse model of AD in which Aβ is deposited in the brain. We used repeated scanning ultrasound (SUS) treatments of the mouse brain to remove Aβ, without the need for any additional therapeutic agent such as anti-Aβ antibody. … Plaque burden was reduced in SUS-treated AD mice compared to sham-treated animals, and cleared plaques were observed in 75%

of SUS-treated mice" (Leinenga & Götz, 2015, p. 1). Mice that were tested "displayed improved performance on three memory tasks: the Y-maze, the novel object recognition test, and the active place avoidance task" (Leinenga & Götz, 2015, p. 1). Previously, "only one method has been demonstrated to open the BBB noninvasively and repeatedly, that is, nonthermal focused ultrasound coupled with intravenous injection of microbubbles, which are used as ultrasound contrast agents" (Leinenga & Götz, 2015, p. 1). Tau protein does play a role because "microtubule-associated protein tau becomes phosphorylated in response to Aβ. … but phosphorylation was too variable to reveal a difference between groups" (Leinenga & Götz, 2015, p. 6). As noted previously, inflammation is also an important factor in neurodegenerative diseases. Leinenga and Götz (2015) determined "no difference between SUS-treated and sham-treated APP23 mice" (Leinenga & Götz, 2015, p. 6) in regards to "SUS up-regulated inflammatory markers associated with tissue damage" (Leinenga & Götz, 2015, p. 6). While SUS shows promise, Leinenga and Götz (2015) do point out that "SUS treatment engages microglia and promoted internalization of Aβ into microglial lysosomes, thereby reducing Aβ and plaque load in the APP23 transgenic mouse model of AD as well as restoring function in tests of spatial and recognition memory. Although we have shown that SUS treatment induces microglial to effectively clear Aβ, it is equally possible that ultrasound and the transient opening of the BBB also attenuates the deposition of newly generated Aβ" (Leinenga & Götz, 2015, p. 7). It is important to note that Leinenga and Götz (2015) stated they did not address this in the study.

Prevention and education of TBIs

There is an abundance of information lending to the hypothesis that repetitive TBI's can contribute to the development of neurodegenerative diseases, in particular PD, AD, and CTE. Furthermore it has been shown that there may be a correlation between early onset AD and

repetitive TBI's. So it would stand to reason that prevention and education about TBI's would be a good step in preventing neurodegenerative diseases.

Prevention of TBI's

The majority of TBI's can be prevented as they occur in contact sports. There is some difficulty estimating the instances of TBI's in the US, as the amount of TBI's suffered range from "300,000 to 3.8 million annually" (Wiebe, Comstock, & Nance, 2011, p. 69). Due to the frequency of TBI's in contact sports, often children are the ones who are injured (Wiebe, Comstock, & Nance, 2011, p. 69). Benson et al., (2013) suggested that there was no conclusive evidence to support that equipment such as headgear or mouth guards prevent TBI's in contact sports, nor does increasing neck strength (Benson et al., 2013, p. 1). When looking at neck strength, this may conflict with the suggestion of Meehan, Taylor and Proctor (2011) that the weaker neck muscles and larger head may play an important role in sustaining a TBI (Meehan, Taylor, & Proctor, 2011, p. 2). When considering headgear and mouth guards, we can see the importance when looking at sports such as bicycling, skiing, and snowboarding, where evidence supports the use of headgear may reduce the risk of a head or brain injury. It is important to note that the use of helmets in football and ice hockey do play a role in preventing severe TBI's as well as skull fractures (Benson et al., 2013, p. 5). Benson et al., did conclude that two of the biggest factors in preventing head trauma are to eliminate body checking in ice hockey with players between 11-12 years of age, as well as implementing an annual awareness program for coaches and referees (Benson et al., 2013, p. 5). The most efficient way to reduce TBI's appears to be further rule changes in contact sports as well as targeted training to reduce impacts to the head while playing sports (Crisco & Greenwald, 2011, p. 2). Crisco and Greenwald (2011) correlated the impact exposure and impact severity and hypothesized "that reducing or limiting

the number and severity of head impacts would result in a decrease in the incidence and severity of clinically relevant cognitive deficits and in the incidence of clinical diagnosis of concussion" (Crisco & Greenwald, 2011, p. 2). To do this, rules of many sports have had to be modified. One of the largest changes suggested would be to eliminate intentional contact with the head in sports, as well as changes in tackling, blocking and checking techniques. Both the NFL and the NHL have adopted rule changes intended to eliminate intentional blows to the head (Crisco & Greenwald, 2011, p. 2). World Wrestling Entertainment (WWE) has also made changes to how their entertainers perform in the ring. WWE donated 1.2 million dollars to The Sports Legacy Institute to further research into developing treatment of CTE. WWE has also eliminated certain moves such as unprotected steel chair shots to the head in hopes of preventing concussions. As of 2006, the WWE also implemented baseline neuropsychology tests for all of their performers, something that is very similar to what the NFL has implemented (Michoces, 2013, p. 1). All of this ties into education about how to recognize and treat TBI's.

Education about TBI's

As noted by Cisco and Greenwald (2011), rule changes in ice hockey for children has been shown to reduce the incidents of TBI's. It therefore stands to reason that early education may be the best key in TBI awareness and prevention. Tator (2012) mentions the five "Es" are essential to prevention of concussion. These five "Es" to prevent injury "include epidemiology, education, engineering, enforcement/legislation of rules, and evaluation of injury prevention programs" (Tator, 2012, p. 293). In support of the argument for more education on TBI's is the fact that many people still believe one needs to lose consciousness to suffer a TBI, when in fact the majority of TBI's suffered occur without any loss of consciousness (Tator, 2012, p. 294). When developing strategies and resources to educate and increase awareness of TBI's, Tator

(2012) suggests that while "approximately 90% of the content is uniform, it is suggested that such information be as sport-specific as possible" (Tator, 2012, p. 295). Some of the ideas that Tator (2012) suggests include TBI road shows, TBI education and awareness committees, concussion cards to help determine if a TBI has been suffered and guidelines for return to play, websites, mandatory TBI education, preseason sports team meetings on TBI education, journal articles/continuing education/webinars, and locker room posters. A great example of the use of locker room posters would be the NFL. In 2010 the league initiated a campaign via locker room posters urging players to report TBI's to team officials (Tator, 2012, p. 296). Tator (2012) suggests a three pronged strategy of primary, secondary and tertiary strategies to prevent TBI's. Initially, "primary strategies are those that prevent concussions from happening. …Secondary prevention refers to expert management of a concussion that has already occurred; such strategies are designed to prevent worsening, such as that which occurs most dramatically with second impact syndrome. Tertiary strategies help prevent the long-term complications of concussion, such as chronic traumatic encephalopathy (CTE) by advising the participant to permanently discontinue play based on evidence-based guidelines" (Tator, 2012, p. 297).

As mentioned previously, early education is key to TBI prevention. With this in mind, the Centers for Disease Control and Prevention (CDC) partnered with experts in the field of head trauma and developed a tool kit that was sent out to high school coaches. This tool kit contained practical and easy to use TBI related information, with the intent of reducing the number of sports related TBI's (Sarmiento, Mitchko, Klein, & Wong, 2010, p. 112). The tool kit included "a guide for coaches, a video, clipboard sticker, wallet card, and fact sheets for parents and athletes. The combined promotional efforts of the CDC, partners, and expert panel members, resulted in more than 20,000 tool kits distributed nationwide within 3 months of its launch"

(Sarmiento et a;., 2010, p. 113). The tool kit materials were also made available free of charge on the CDC's website (Sarmiento et al., 2010, p. 113). The focus of Sarmiento et al., (2010) study was quite simply, did this tool kit obtain the desired results and how well did this tool kit work to reduce the instances of TBI amongst athletes. The majority of coaches did feel that the information provided by the CDC tool kit was more comprehensive than current policies in place at their schools, but there were barriers to education and TBI management that were mentioned. Some of these barriers include parents' and/or athletes' competitiveness, underestimating the potential risks of concussions, lack of health insurance, and viewing injuries as a sign of weakness. Sarmiento et al., (2010) makes note that one of the biggest barriers has been parents and their reluctance to take an injury seriously unless their child is bleeding profusely or a bone is broken (Sarmiento et al., 2010, p. 115). One of the most important results of the distribution of this tool kit was the fact that "half of survey respondents (50%) reported that the tool kit changed their views on the seriousness of concussions. Of those coaches who noted a change, all of them reported that they now regard concussions more seriously" (Sarmiento et al., 2010, p. 115). An important aspect covered by Sarmiento et al., (2010) is the subject of rest and limiting activities during the recovery period of a TBI. Even activities that may not be physically demanding such as studying, playing video games or working on the computer may cause TBI symptoms to reappear or worsen. Sarmiento et al., (2010) also mentions what is called cognitive exertional effects, which is seen when TBI symptoms worsen when doing schoolwork. Thinking and learning, both cognitive activities, "must be carefully monitored and managed to prevent this from happening. Students who return to school after a concussion may need to take rest breaks as needed, spend fewer hours at school, be given more time to take tests or complete assignments, receive help with school work, and reduce time spent on the computer, reading, or writing"

(Sarmiento et al., 2010, p. 117). It also is very important not to return to any physical activity until the athlete is symptom free and medically cleared (Sarmiento et al., 2010, p. 117). The reason this is so important is the fact that this is an important step to avoid second impact syndrome. Something else that is very important is speaking with the athlete about the effects of a TBI, what the athlete may experience emotionally and physically and offer encouragement and support during this time (Sarmiento et al., 2010, p. 117).

Conclusion

As we have seen, neurodegenerative diseases/disorders are a wide umbrella. My focus was primarily on head trauma as the cause, but it has been hypothesized that genetics may play a role as well. Regardless of the cause, there is no doubt that neurodegenerative diseases are debilitating and take a toll not only on the person suffering from the disease but also their family and friends. I did focus on Parkinson's disease (PD), Alzheimer's disease (AD) which is usually associated with progressive dementia, and Chronic Traumatic Encephalopathy (CTE) because these three diseases have been linked to traumatic brain injury (TBI) in a number of studies. Presently there is no way to conclusively determine if someone is suffering from one of these diseases until a post mortem examination of the brain is conducted, although there are symptoms common to these diseases where we may see an indication of what to expect upon examination. When a TBI occurs, a cascading set of events results in glutamate toxicity, beta-amyloid (Aβ) protein plaque buildup and neurofibrillary tangles of tau protein buildup within the cells. As these elements build up in the brain, neurons degenerate and die.

There are new treatments on the horizon that may treat the symptoms, and in some cases possibly break up the Aβ protein plaques. My goal was to focus on alternative or new treatment methods such as nanotechnology, medicinal marijuana, stem cell research and ultrasound

treatment. The most controversial in the United States would be medicinal marijuana and stem cell treatments due to government regulation and ethical complications, but I believe with time we will see the potential of these ground breaking methods opening up the doors to more research. More recently we have seen promise in repeated scanning ultrasound (SUS) where when used on mice, SUS broke up the Aβ plaques and a majority of the mice regained memory that was previously lost due to AD symptoms. While the focus was mice with symptoms of AD, AD and CTE are closely linked in a number of ways, so this method may show promise with other neurodegenerative diseases as well.

Possibly the most important tool we have in the fight against neurodegenerative disease and TBI is education and prevention. We have already seen major strides made in both of these areas, but we do still have a long way to go. Major sports leagues and promotions have taken the lead not only in donating money to research, but also in prevention of TBI's by changing the rules of their respective sports. We have seen the implementation of neuropsychology tests, reporting of TBI's, education of the short term and long term effects of a TBI, and why it is so important to not continue to compete while suffering the symptoms of a TBI in sports leagues such as the NFL, NHL, and WWE amongst others. But is this enough? The CDC distributed a "Heads Up" tool kit to high school coaches to help educate coaches, players and their parents of the effects of TBI's, and we have seen some success, although there are barriers that we must overcome. We will always see athletes who do not want to take themselves out of the game. Athletes by nature are competitive and often times stubborn and rarely will pull themselves from competition, so this barrier is not unexpected. Surprisingly though, one of the barriers to preventing TBI's in young athletes are parents that do not take TBI's as seriously as they should. When one considers the possible link between repetitive TBI's being linked to early onset AD

and dementia as well as CTE, and the impact these diseases have on the families of the athletes suffering from these diseases, it is evident that while we have made great strides in education and prevention of TBI, there still is progress that can be made.

For a long time, those whom suffered the effects of TBI's and later developed a neurodegenerative disease suffered in silence. No one wanted to admit they suffered from anxiety. No one wanted to admit they suffered from depression. People knew something was wrong, but didn't know what it was. They couldn't sleep properly, suffered headaches regularly, suffered memory loss as well as deficits in other cognitive abilities and other various symptoms. It was only recently that we now know why and we can at least provide some relief to those suffering if they ask for help. We are now seeing people asking for help, which that in itself is an improvement. So while we have come a long way in the field of neurodegenerative disease and head trauma, we do still have a long way to go.

Abstract

Figure 1. (McKee et al., 2013, p. 46)

Table 1 Distinctions in hyperphosphorylated tau pathology between Alzheimer's disease and CTE

Pathological features	Alzheimer's disease	CTE
Tau protein		
Six isoforms	All six isoforms present	All six isoforms present[a]
3 or 4 repeat tau	3 repeat and 4 repeat tau present	3 repeat and 4 repeat tau present
Cell origin		
Neuronal	NFTs and pre-tangles	NFTs and pre-tangles
Astrocytic	Not present[b]	Prominent astrocytic tangles
Neuronal domain		
Cell body	Prominent	Prominent
Dendrite	Prominent	Prominent
Axon	Sparse	Prominent
Cell Pattern		
Perivascular	Not present	Prominent NFTs and astrocytic tangles
Foci at depths of cerebral sulci	Not present	Prominent NFTs and astrocytic tangles
Irregular, patchy cortical distribution	Not present	Prominent
Cortical laminae	NFTs predominantly in laminae III and V	NFTs predominantly in laminae II–III
Subpial astrocytic tangles	Not present	Prominent
Periventricular astrocytic tangles	Not present	Present
Distribution		
Mild pathology	Braak stages I–III: NFTs in entorhinal cortex, amygdala and hippocampus	CTE stages I–II: NFTs in focal epicentres in cerebral cortex, usually frontal lobe
Advanced pathology	Braak stages IV–VI: High density of NFTs in widespread cortical areas and medial temporal lobe, uniform distribution Low densities of NFTs in basal ganglia and brainstem; none in mammillary bodies. White matter tracts relatively uninvolved.	CTE stages III–IV: High density of NFTs in widespread cortical areas and medial temporal lobe, patchy irregular distribution High densities of NFTs in thalamus, hypothalamus, mammillary bodies, brainstem. Moderate densities of NFTs in basal ganglia, especially nucleus accumbens. Prominent p-tau pathology in white matter tracts.

Figure 2. (Tanveer, McGuinness, Daniel, Gowran, & Campbell, 2012, p. 634)

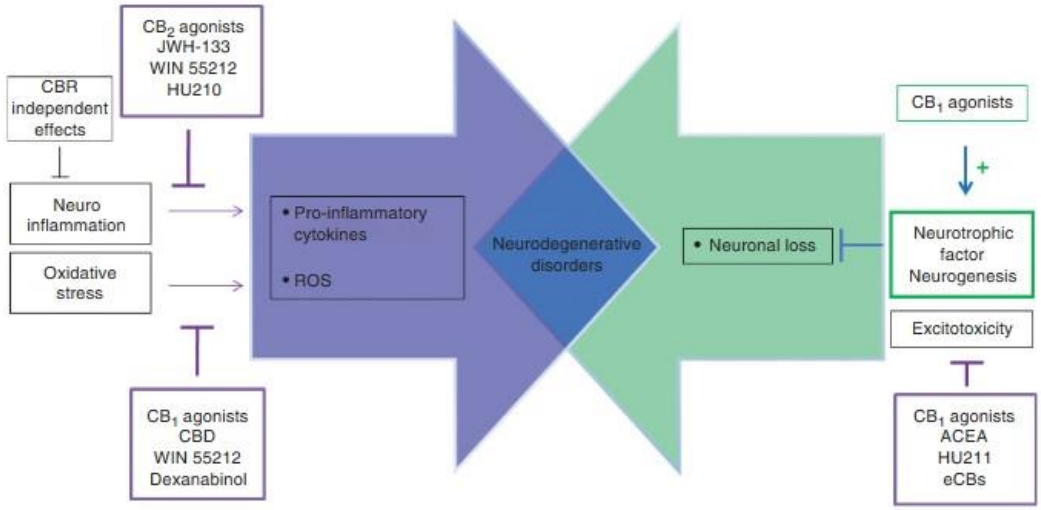

FIGURE 1 | Schematic model of neurodegenerative disorders and possible sites of intervention by drugs that modulate the endocannabinoid system. Modulators of the endocannabinoid system affect the function of neurones and microglia to induce an environment that is anti-inflammatory (purple arrow) and supportive of neurogenesis and repair (green arrow). This approach targets the common events associated with the selective loss of vulnerable subpopulations of neurones that is linked to the cognitive instability associated with neurodegenerative disorders. Activation of the CB_1 receptor inhibits excitotoxic glutamate signaling and ROS production, whilst also enhancing the expression of neurotrophic factors such as BDNF. Targeting the CB_2 receptor is more appealing because CB_2 agonists lack psychoactivity and can regulate the immunomodulatory cells of the CNS. Additionally $CB_{1/2}$ receptor independent effects of cannabinoids may be indicative for the existence of undiscovered CB receptor types capable of mediating neuroprotection. CB, cannabinoid; CBD, cannabidiol; eCBS, endocannabinoids; ROS, reactive oxygen species.

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