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# Propranolol: a Treatment for Posttraumatic Stress Disorder (Ptd) Or a Breach in Neuroethics?

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PROPRANOLOL AND PTSD

**PROPRANOLOL:**  
*A TREATMENT FOR POSTTRAUMATIC STRESS DISORDER (PTSD)*  
*OR A BREACH IN NEUROETHICS?*

A thesis submitted to  
Regis College  
The Honors Program  
in partial fulfillment of the requirements  
for Graduation with Honors

by

Joshua R. Kniss

May 2012

Thesis written by

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Director, University Honors Program

# PROPRANOLOL AND PTSD

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**The Preface:**  
**A thesis is more than a document to be read...**

“I hope that my achievements in life shall be these—  
that I will have fought for what was right and fair,  
that I will have risked for that which mattered, and  
that I will have given help to those who were in need,  
that I will have left the earth a better place for what  
I’ve done and who I’ve been.”

*~ C. Hoppe*

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Four years ago, I first stepped foot on the Regis University campus, and since that time I have experienced many different thoughts, ideas, and theories that have ultimately lead to this thesis. My time at Regis has been a time of learning both inside and outside of the classroom. My academic path through Regis has primarily revealed itself through the combination of three avenues of learning: an education in neuroscience, the liberal arts core curriculum, and the honors program curriculum. In addition to these avenues of learning, I have also learned a great deal outside of the classroom through conversations with other members of the Regis community, as well as my involvement on campus. The goal for this thesis is to draw upon all aspects of my education, both academic and non-academic, as well as integrate the values and beliefs that are at the core of who I am as a human being.

The most influential portion of my life for the last four years has been the time I have spent at Regis University. Most of my time at Regis has been spent in the classroom or studying, as it should be; and most of my time in the classroom has been spent in the neuroscience department, as it should be. All kidding aside, I have gained a tremendous appreciation for the human brain, the nervous system, and how these structures influence who we are as people during my time at Regis. As a result of these interests, neuroscience has become my major,

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the focus of my education for the past few years, and now a primary focus of my thesis project.

Although neuroscience has played a major role in my academic career, the summation of all my areas of study has determined my overall, Regis education. Regis University has a rather vast core curriculum, as it is a liberal arts college. At times this has been a burden, as I would prefer to spend my time in the neuroscience laboratory, but in retrospect, I am glad for the numerous disciplines I have encountered. Regis emphasizes the importance of a well rounded individual, and the core curriculum is one way of accomplishing this emphasis. A person is only able to be knowledgeable in the world by knowing a little of everything, and it is often true that one discipline will inform another, further enhancing an individual's intellectual prowess. I have learned that interdisciplinary learning is the most challenging, but also the most rewarding and applicable to the real world. Because of this, I have aimed to create an interdisciplinary thesis, in which I not only approach a neuroscience topic but some other aspect of the topic as well.

The final avenue of learning that has guided me through my education at Regis has been the honors program. The honors program curriculum is interdisciplinary in nature, but is also more than that. The honors program

emphasizes the importance of asking one's self very difficult questions. Such questions include: how can tradition inform innovation, what is justice, and how does one find meaning? These questions do not have universal answers, but they must be thought about because of the ways that they inform an individual's life. Whether conscious or not, every individual must have a meaning for their life as well as a clear conception of what is just. Without these beliefs, no individual could carry out simple everyday tasks such as waking up in the morning or going to work. One must have a purpose for his or her life, and then carry his or her passion into all the work that he or she takes part in. Likewise, a person must know how to live justly through his or her work, friendships, and every day interactions. In summary, the honors program has helped me solidify my own beliefs and encouraged me to continue asking questions that may or may not have answers. In regards to this thesis, the honors program has confirmed my belief that it must be interdisciplinary, but it also directed me to look for a thesis topic that I find personally important.

Bringing all three of these avenues into conversation, I concluded that this thesis should attempt to answer a challenging question, be interdisciplinary in nature, be grounded in neuroscience, and most of all, be of value to me. In order

to narrow in on the topic of this thesis, posttraumatic stress disorder, I looked to my experiences outside the classroom.

A major influence in my life is my family, and a good portion of my family is military. Additionally, I have thought heavily about joining the military as I pursue a career as well. Thus, the military seemed to be an appropriate area to explore. With some research and a lot of thought, I began to investigate posttraumatic stress disorder. Through my neuroscience background, I had been exposed to the tragedies of the disorder and the impairments that it may cause, but it was not until I began investigating the disorder apart from neuroscience and psychology that I fully realized the issues surrounding the disorder. For instance, veterans and legislators have been in a heated agreement over the question: should war veterans with PTSD be given a purple heart? This further leads to an even greater question, how is physical injury different from mental injury? The answer to this question is not easily answered, but it is generally agreed upon that mental injury is indeed different than physical injury. Physical injury, no matter how severe, will not change the person's personality, perceptions, or memories unless there is a mental side effect to the physical damage. On the contrary, mental injury has a great impact on all these aspects of the person's identity. From this stance, I decided to explore the possibilities of

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treating PTSD. In almost all circumstances, a person will correct a physical injury if possible. With PTSD, however, this is not an option. Although there is ample research looking into treatments for PTSD, there currently is not a treatment to prevent or relinquish PTSD symptoms. Due to my personal connection to the military, I decided to contribute to PTSD research and study the effects of propranolol (an experimental drug) on PTSD symptoms. In short, I see the ultimate goal of PTSD research, and my thesis, as helping those suffering from PTSD cope with the disorder and possibly restore their pre-trauma quality of living.

The foundation of my thesis is to experimentally test the effects of propranolol as it relates to PTSD symptoms. However, this does not fulfill all the requirements I had set for myself in creating this thesis project. From the time I began proposing my experiment, I also began to question the possible impacts of a drug that would treat PTSD. How could a drug simply wipe away one's memory or completely dissociate the emotional impact of such a memory? And if this could really happen, should it? Much of my life has been informed by the memories I have. I believe that I am not simply one person, but a summation of every person I have been at each point in my life. In other words, I am who I am because of my experiences; my value of memory is very high. Thus a personal

conflict arises. I have a desire to help suffering individuals, but through certain forms of helping, one may remove key elements of that person's identity and alter his or her future self. At this cost, is treating the disorder still *helping*? In this conflict, I discovered the second portion of this thesis. Through asking tough questions, such as what is the value of suffering, how can one give informed consent for such a treatment, and how does religion impact such a treatment decision, I decided to explore whether treating PTSD would be ethically possible, and if so, would the treatment of PTSD bring justice to the victim.

This thesis is my attempt to give attention to a topic that is controversial, but also deeply rooted in the lives of many. At the conclusion of this thesis, I would like to have a universal answer to the questions I have raised, but I cannot guarantee this will be the result. What I can guarantee is that I will have a greater understanding of the topic and will have insights that I did not have at the start of this project. I also hope that you gain a better understanding of the topic at hand as a result of my work here. It is true that a thesis is more than a document to be read. A thesis springs from a need or question in the world, and has the potential to create a change. In conclusion, I propose that we all ask the tough questions and begin to seriously consider the impacts of the decisions we make

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whether they be monumental, such as treating a patient with PTSD, or every day, such as helping a neighbor in need.

**An introduction to posttraumatic stress disorder (PTSD):  
The history, etiology, and treatment strategies**

The popular expression “What does not kill you makes you stronger” points to some people’s ability to respond to trauma resiliently. However, for those same traumas, a more appropriate statement may be “What does not kill you can make you ill” or “What does not kill you might as well have.” There are many individuals who are not resilient to trauma, and when faced with a traumatic experience, their lives are forever altered. Even those who are highly resilient may develop a serious psychological disorder depending on the severity of the trauma. Approximately one tenth of those who survive life-threatening events will develop a mental health disorder, such as posttraumatic stress disorder (PTSD) (Jovanovic & Ressler, 2010). Although PTSD was once thought to be relatively uncommon, recent estimates suggest that between 10 and 39 percent of all people will suffer from PTSD during their lives (Cantor, 2005, p.7). PTSD is a serious issue, and is one that needs to be addressed.

Although the diagnostic criteria for PTSD have only been in place since 1980, the symptoms associated with PTSD have been around for much longer. Symptoms associated with PTSD, such as high levels of anxiety, heightened startle response, nightmares, and emotional reliving of experiences have existed since the pre-Christian period (Parry-Jones & Parry-Jones, 1994). Although PTSD is no longer a new term, the disorder has been around for a much longer period

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under other pseudonyms. Since the mid-nineteenth century, PTSD-type symptoms have been given numerous titles such as: spinal concussion, railway spins, and irritable heart from the 1860s; soldier's heart and cardiac weakness from the 1870s; traumatic shock, traumatic neurosis, hysterical hemianaesthesia, spinal irritation, railway brain, and nervous shock from the 1880s; anxiety neurosis and psychological trauma from the 1890s; traumatic neurosis, shell fever, irritable heart of soldiers, mental shock, war shock, shell shock, neuro-circulatory asthenia, disordered action of the heart, and war psychoneurosis from the 1910s; cardiac/war neurosis from the 1930s; and battle fatigue/combat exhaustion and effort syndrome from the 1940s (Parry-Jones and Parry-Jones, 1994). Each of these terms referred to what is now known as posttraumatic stress disorder. It was not until 1980, when posttraumatic stress disorder was added to the third edition of the Diagnostic and Statistical Manual for Mental Disorders that PTSD became a generally accepted term for such abnormal responses to severe trauma (Cantor, 2005).

The Diagnostic and Statistical Manual for Mental Disorders (DSM-IV-TR) provides the following diagnostic criteria for PTSD (2000). For an individual to be diagnosed with PTSD, the person must have been exposed to a traumatic

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event in which the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others. Additionally, the person's response to the experience must involve intense fear, helplessness, or horror. The victim must also persistently re-experience the traumatic event through visual images, thoughts, dreams, or mental recreation of the event. The person must avoid stimuli associated with the trauma and have persistent symptoms of increased arousal. Finally, the duration of the disturbance must be more than one month (American Psychiatric Association [DSM-IV-TR], 2000). These are the symptoms that an individual must present to be classified as experiencing PTSD.

PTSD-influencing traumas are more common than one may think. Such traumatic experiences do not only happen during war or high conflict situations, but also during everyday life. For example, several of the earlier terms for PTSD involved the railway due to the traumatic scenes of train crashes during that time period. One notable victim of such a crash was Charles Dickens. A train crash left his carriage swaying precariously from a bridge, and upon emerging from his carriage he was greeted with the sight of dead and injured all around him (Cantor, 2005). Although PTSD was not recognized as a diagnosis at the time,

Charles Dickens' experiences in the train crash nearly 150 years ago closely resemble what many sufferers of acute stress and PTSD go through today.

Although people who have been tortured and/or victimized for long periods of time suffer the highest rates of PTSD and that prisoners of war and concentration camp survivors have a 50% rate of chronic PTSD, the prevalence of PTSD resulting from other everyday-type traumatic experiences is significant as well (Cantor, 2005). Civilians too face surprisingly high rates of exposure to traumatic stressors during their normal, everyday routine, including rape, terrorist attacks, death of a loved one, childhood abuse, natural disasters, and a wide variety of other severe psychological traumas (Heim & Nemeroff, 2009). Survivors of natural disasters have rates of PTSD around 4% (Cantor, 2005). 12% of individuals involved in a motor vehicle accident, which has a lifetime prevalence of 23%, develop PTSD (Cantor, 2005). Assault is another trauma which may result in PTSD. Thirty percent of non-sexual assault case victims and 50% of rape victims will develop PTSD within three months of the trauma (Cantor, 2005). Traumas associated with war and combat are leading causes of PTSD, but traumas of everyday life also lead to PTSD symptoms. These PTSD causing traumas are linked by their uncontrollability.

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When all the possible PTSD-producing traumatic events are summed together, the prevalence of PTSD shows itself to be quite high. Posttraumatic stress disorder is a serious anxiety disorder with a lifetime prevalence of approximately 6.8% in the United States and a 12 month prevalence of 3.8% (Adamec, Muir, Grimes, & Pearcey, 2007). Given that 50-60% of all North Americans experience a traumatic stress in their lifetimes, and 15% of these traumatically stressed individuals will subsequently develop PTSD, PTSD has become a serious issue and the topic of much research (Adamec, Muir, Grimes, & Pearcey, 2007). Further enhancing the need for a better understanding of PTSD is the fact that approximately 30% of patients experiencing PTSD will still be suffering from the disorder at least ten years after the trauma (Langevin, De Salles, Kosoyan, & Krahl, 2010). This is highly troubling because research has shown that if PTSD symptoms have not been resolved within 6 years, the symptoms are highly likely to remain chronic (Cantor, 2005).

Currently, the three most common treatment methods for PTSD are cognitive behavior therapy, eye movement desensitization and reprocessing (EMDR), and stress management (Ponniah & Hollon, 2009). Trauma-focused cognitive behavior therapy involves repeated exposure to the traumatic memory

through cognitive methods and then progressively changing the individual's thought processes and behaviors towards the trauma. EMDR utilizes dual attention tasks to help the patient process the traumatic event. EMDR involves the patient focusing on negative trauma-related memories while engaging in a task involving some form of bilateral stimulation, such as eye movements, until distress has decreased and belief in more positive trauma-related thoughts has increased. Stress management does not focus on the trauma, but involves the patient's learning skills to help manage anxiety. Such skills consist of slow, abdominal breathing, relaxation techniques, learning to use positive statements and self-talk strategies, distraction techniques, and assertiveness training.

Although these three treatments prove helpful for some patients suffering from PTSD, 30% of patients who develop PTSD will still be suffering from treatment ten years following the trauma (Langevin, De Salles, Kosoyan, & Krahl, 2010, p. 1241). This prevalent rate reflects that the current treatments for PTSD do not meet all of the needs of those affected. Although there have been significant advances in the understanding of PTSD, treatment failures persist. As a result, researchers have subsequently begun studying the effects of possible pharmacological interventions.

While the goal of any study focusing on a disease or disorder is to find a cure, the mechanisms through which the disorder or disease arises must first be understood so that an effective treatment may be found. It is generally accepted that the symptoms of PTSD reflect stress-induced changes in neurobiological systems and/or an inadequate adaptation of neurobiological systems to exposure of severe stressors. However, it is not clear which specific neurological systems, neurotransmitters, or brain structures are affected by the traumatic experience(s), and subsequently, elicit PTSD.

Various aspects of the nervous system have been implicated in the pathophysiology of PTSD, including the hypothalamic-pituitary-adrenal (HPA axis), the hippocampus, the amygdala, the prefrontal cortex, as well as six neurotransmitters and neuropeptides. Each of these brain structures, systems, and neurotransmitters play a role in the regulation of fear, the response to stress, or memory consolidation, and have attracted much attention regarding the study of the etiology of PTSD and the any potential treatments for the disorder.

The neurocircuitry that has been scrutinized most closely in PTSD patients has been the HPA axis, an organism's major neuroendocrine stress response system (Heim & Nemeroff, 2009), which is responsible for coordinating the

body's response to stress (Yehuda, 2000). Upon exposure to a stressor, neurons in the hypothalamic paraventricular nucleus (PVN) secrete corticotrophin-releasing factor (CRF). CRF is then transported to the anterior pituitary where it stimulates the production of adrenocorticotropic (ACTH). ACTH, in turn, stimulates the release of glucocorticoids from the adrenal cortex. Glucocorticoids exert effects on metabolism, immune function, and the brain to adjust physiological functions and behavior to the stressor (Heim & Nemeroff, 2009). In short, a stressor affects a cascade of hormones that eventually results in the release of cortisol from the adrenal cortex, which functions to manage the body's biological stress response by stimulating the termination of neural defense reactions that have been activated by stress (Yehuda, 2000). These mechanisms cause the HPA axis to be the major system in which trauma is managed.

Studies of the HPA axis in patients with PTSD have revealed low cortisol levels in patients with PTSD regardless of the type of trauma, an individual's age at traumatization, the duration of PTSD symptoms, or the age of the subjects at the time of biological assessment (Heim & Nemeroff, 2009; Yehuda, 2000).

Cortisol serves a regulatory function in the CNS. Decreased cortisol levels result in PTSD because less cortisol equates to an individual's lessened ability to

manage their biological response to trauma. This inability to manage one's biological response to trauma results in the sustained activation of neural systems involved in stress reactivity and fear processing (Heim & Nemeroff, 2009). All considered, it seems that cortisol levels are directly associated with the severity of PTSD symptoms.

Several brain pathways modulate HPA axis activity. The hippocampus and prefrontal cortex inhibit the HPA axis, whereas the amygdala and monoaminergic input from the brainstem stimulate the activity of neurons associated with the HPA axis (Heim & Nemeroff, 2009), creating an interest in these pathways as well. The most reproducible finding in structural imaging studies of PTSD is reduced volume of the hippocampus. The hippocampus is implicated in the control of stress responses, declarative memory and contextual aspects of fear conditioning (Heim & Nemeroff, 2009). A preponderance of neuroimaging data from the past decade demonstrates that PTSD patients have greater amygdala activation relative to comparison subjects; brain imaging studies (PET and fMRI) have found that the amygdala modulates the fear response (Jovanovic & Ressler, 2010). Furthermore, recent functional magnetic resonance imaging (fMRI) studies have found that trauma-relevant words as

well as trauma-specific imagery increase amygdala activation (Jovanovic & Ressler, 2010). In much the same way, the prefrontal cortex is implicated in PTSD. Recent studies have demonstrated that neurons in the prefrontal cortex have inhibitory action on the amygdala (Jovanovic & Ressler, 2010). Exaggerated fear responses observed in PTSD and the impaired inhibition on conditioned inhibition tasks is thought to be due to a weakened inhibitory control of the amygdala by the prefrontal cortex in combination with a lack of control over stress responses due to alterations in hippocampal volume. Ultimately, several brain regions are currently implicated in PTSD.

Yet, like most mental disorders, it is likely that the unfavorable stress response to a traumatic event in PTSD is influenced by an imbalance in neurotransmitters, whether due to overproduction, inactivation, or an alteration at the receptor sites. Several neurotransmitters and neuropeptides are involved in the body's response to stress, and thus, are of interest in PTSD research. The implicated neurotransmitters are norepinephrine, serotonin, GABA, glutamate, neuropeptide Y, and opioids (Heim & Nemeroff, 2009). Norepinephrine is believed to play the greatest role in an individual's response to trauma and the memory consolidation of such trauma.

Before discussing norepinephrine, the effects of serotonin, GABA, glutamate, neuropeptide Y, and opioids as related to PTSD symptoms should be discussed. Serotonin helps to regulate sleep, appetite, sexual behavior, aggression and impulsivity, motor function, and neuroendocrine control (Heim & Nemeroff, 2009). Serotonin neurons of the dorsal raphe projecting to the amygdala and hippocampus mediate stress-increasing effects via serotonin receptors (Heim & Nemeroff, 2009). Chronic exposure to stressors induces upregulation of these serotonin receptors (Heim & Nemeroff, 2009). Altered serotonin transmission may contribute to a subset of the symptoms of PTSD that includes hypervigilance, increased startle response, impulsivity, and intrusive memories. Additionally, treatment with GABA agonists decreases symptoms of anxiety in PTSD, and exposure to stressors increases glutamate release in the brain (Heim & Nemeroff, 2009). Neuropeptide Y inhibits CRF and norepinephrine circuits involved in stress and fear responses (Heim & Nemeroff, 2009). Thus, a lack of neuropeptide Y promotes a maladaptive stress response and contributes to the development of PTSD (Heim & Nemeroff, 2009).

Endogenous opioids such as endorphins or enkephalins inhibit the HPA axis, and alterations are involved in symptoms of numbing, stress-induced analgesia, and dissociation in PTSD (Heim & Nemeroff, 2009). Opiates have the ability to

dampen central noradrenergic hyperactivity, and consequently PTSD symptoms (Strawn & Geraciotti, 2008). Clearly, neurotransmitters are not without an effect on the development and sustainment of PTSD.

The major stress response neurotransmitter is norepinephrine.

Norepinephrine is the major central catecholamine, and is derived from neurons of the locus coeruleus. These neurons project to many structures that are involved in the pathophysiology of PTSD. Structures affected by norepinephrine include the prefrontal cortex, amygdala, hippocampus, hypothalamus, periaqueductal gray matter and thalamus (Liberson et al., 1999; Phan et al., 2006; Pissiotta et al., 2002). Norepinephrine largely affects the regulation of arousal and autonomic stress responses. Norepinephrine (NE) is produced by the adrenal medulla through sympathetic stimulation and the local effects of cortisol, and provides positive feedback to the pituitary gland maintaining the stress response and further stimulating the HPA axis (Vermetten & Bremner, 2002).

Norepinephrine is also thought to play a role in the encoding of memories (Vermetten & Bremner, 2002). Norepinephrine exerts its effects by binding to alpha or beta adrenoceptors. Beta receptors are linked to G-protein systems, and promote its effects by the increase of adenylyl cyclase. In contrast, alpha

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receptors are associated with a myriad of biochemical effectors; alpha receptors effects are also transduced through a G-protein system (Strawn & Geraciotti, 2008). To reduce the effects of norepinephrine at each of these receptors, antagonists for each of the receptors may be introduced. Although antagonist for alpha as well as beta receptors have proved effective at reducing the effects of norepinephrine, beta blockers are more centrally acting (Strawn & Geraciotti, 2008). Norepinephrine has been a central candidate in studying the pathophysiology of PTSD (Heim & Nemeroff, 2009).

Combat veterans, abused women, and children with PTSD have increased levels of norepinephrine in their urine (Heim & Nemeroff, 2009). A couple of studies have investigated the excretion of catecholamines following sexual abuse. De Billis et al. (1994) found increased levels of norepinephrine 24 hours after the abuse, and Lemieux and Coe (1995) documented increased levels of norepinephrine excretion later in life for the individuals who go on to develop PTSD related to childhood sexual abuse. Likewise, combat veterans with PTSD show increased levels of norepinephrine excretion 24 hours after trauma compared to patients with major depression, bipolar mania, paranoid schizophrenia, undifferentiated schizophrenia, and healthy control subjects

(Kosten et al., 1987; Yehuda et al., 1992). While many studies have assessed urinary concentrations of norepinephrine, not all of them have observed increased levels of norepinephrine in patients with PTSD (Glover and Loland, 2002). This finding is likely due to norepinephrine's inability to cross the blood-brain barrier. Peripheral concentrations do not well reflect norepinephrine concentrations (Strawn & Geraciotti, 2008). Patients with PTSD have tonically elevated norepinephrine concentrations in the central nervous system, and central nervous system norepinephrine is robustly secreted in response to acute psychological stress (Geraciotti et al., 2001). Clinically, evidence shows that norepinephrine plays a role in an individual's response to stress, and if PTSD develops, increased amounts of norepinephrine are produced.

Based on its strong role in the body's stress response systems, norepinephrine has been a central target in researchers' attempts to develop a preventative treatment for PTSD. One of these norepinephrine-targeting drugs is a long-chain beta-blocker called propranolol. Propranolol is a non-selective beta-adrenergic antagonist that binds to peripheral and central  $\beta$ -adrenergic receptors and readily crosses the blood-brain barrier (Vaiva et al., 2003). Thus, propranolol may be used to block  $\beta$ -noradrenergic receptors in the amygdala after fear

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memory training blocks consolidation of the fear memory. Although attempts to mitigate PTSD symptoms with post stressor block of  $\beta$ -noradrenergic receptors with propranolol have been successful (Pitman et al., 2002; Reist et al., 2001; Vaiva et al., 2003), some research has found propranolol ineffective in treating PTSD symptoms (Cohen et al., 2011). For example, Pitman et al. (2002) reported that propranolol given within 6 hours of a traumatic event for 10 days was superior to a placebo for reducing PTSD symptoms 1 month after trauma. Similarly, Vaiva and colleagues (2003) found that when compared to eight traumatized patients who did not receive propranolol, only one in 11 treated patients developed PTSD two months after the trauma, whereas PTSD developed in three of the eight untreated patients. Evidence has been reported that administration of propranolol shortly after exposure to psychological trauma reduces PTSD symptom severity and reactivity to reminders of the traumatic event (Heim & Nemeroff, 2009). The present study will test propranolol as an experimental treatment for PTSD as defined in a rat model.

Although several studies have experimentally tested PTSD in human trauma victims and the results have shown to affect PTSD symptoms, the

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research is not conclusive that propranolol is an effective treatment to prevent PTSD. This study will attempt to influence an animal model of PTSD, and subsequently test propranolol as a preventative treatment for PTSD-like symptoms in rats exposed to a life-threatening stressor.

The criteria for influencing PTSD in an animal model should include the same criteria as deemed necessary for a diagnosis of PTSD by the DSM-IV-TR. There should be the application of direct physical stressors in conjunction with exogenous stimuli that closely mimic those seen in nature. Furthermore, the stressors should influence a fear for one's life. When these criteria are followed, stressed rats tend to show PTSD-like behavior such as increased immobility, decreased grooming and rearing, decreased exploratory behavior and decreased food consumption (Kesner et al., 2009). Thus, fear conditioned behavior, which is similar to PTSD symptoms, should be able to be accomplished via the implementation of appropriate stressors. It should be noted that chronic PTSD cannot be elicited in animals due to the ethical constraints that are put on the mistreatments that may be put on animals for scientific purposes. In most cases, conditioned fear is taken as the animal model of PTSD.

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The present study will first strive to develop an animal model of PTSD in rodents, and then attempt to evaluate the effects of propranolol on PTSD-like symptoms. In the present study, rats will be exposed to inescapable shocks at a rate of one shock per thirty seconds for ten minutes on a variable interval schedule. This direct stressor will be paired with the scent of bobcat urine in order to create a trauma eliciting PTSD. Rodent behavior - levels of anxiety, burying behavior, and freezing behavior - will be observed pre- and post- trauma to indicate whether rat behavior has changed in response to the traumatic experience. Given that the rodent behavior does change, propranolol will then be used as a treatment for PTSD symptoms. All in all, this study will address three guiding questions for the research: 1) Can an accurate animal model for PTSD be developed? 2) Does propranolol, a  $\beta$ -noradrenergic antagonist, reduce PTSD symptoms? 3) Does propranolol reduce PTSD symptoms via the blockage of  $\beta$ -noradrenergic receptors in the brain?

My hypotheses are that (1) PTSD behavior will be altered in response to a traumatic experience, and subsequently that symptoms similar to PTSD behavior can be observed in an animal model, (2) propranolol will effectively reduce the

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severity of PTSD symptoms, and (3) propranolol prevents the development of PTSD through interference with adrenergic receptors in the amygdala.

**THE EFFECTS OF PROPRANOLOL,  
A NON-SELECTIVE  $\beta$ -ADRENERGIC ANTAGONIST,  
ON RAT BEHAVIOR IN AN ANIMAL MODEL OF  
POSTTRAUMATIC STRESS DISORDER**

Joshua R. Kniss and Mark Basham, Ph.D.

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*Abstract:* To date, very little is known about the neurocircuitry of posttraumatic stress disorder, and currently 5.2 million people are suffering from PTSD in the United States alone. In hopes to treat PTSD symptoms, researchers have targeted corticosteroids, beta-adrenergic antagonists, and opiate analgesics to reduce hormonally enhanced memories and fear conditioning. This study focuses on testing propranolol, a beta-adrenergic antagonist, as a treatment for PTSD-like symptoms (anxiety and freezing behavior) in a rat model. Rats were exposed to inescapable, moderate shocks paired with a predator scent to elicit PTSD-like symptoms. Propranolol was shown to effectively reduce anxiety at 28 days post stress, but did not affect freezing behavior. Through this study, data concerning the time course for PTSD in an animal model was obtained.

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*Key words: posttraumatic stress disorder; norepinephrine; propranolol;  $\beta$ -blocker*

## 1. Introduction

The popular expression “What does not kill you makes you stronger” points to the fact that some people respond to trauma resiliently. While this response may be true for highly resilient people, a more appropriate general statement may be “What does not kill you can make you ill” or “What does not kill you might as well have.” Many individuals are not resilient to trauma, and when faced with a traumatic experience, their lives are forever altered. Even those who are highly resilient may develop a serious psychological disorder contingent on the severity of the trauma. Approximately one tenth of those who survive life-threatening events will develop a mental health disorder, such as posttraumatic stress disorder (PTSD) (Jovanovic & Ressler, 2010). This equates to 5.2 million people suffering from PTSD in the United States (Adamec, Muir, Grimes, & Pearcey, 2007).

In general terms, PTSD is a debilitating psychological condition triggered by a major traumatic event. In addition to war, the stereotypical traumatic experience leading to PTSD, civilians in modern societies also face surprisingly high rates of exposure to traumatic stressors, including rape, terrorist attacks, the

death of loved ones, childhood abuse, natural disasters, and several other severe psychological traumas (Heim & Nemeroff, 2009). Whatever the trauma, all traumatic events are marked by uneasy memories or thoughts of the ordeal, emotional instability, increased arousal, and/or personality changes (Heim & Nemeroff, 2009). However, additional symptoms may develop.

The Diagnostic and Statistical Manual for Mental Disorders (DSM-IV-TR) provides diagnostic criteria for PTSD (American Psychiatric Association [DSM-IV-TR], 2000). For an individual to be diagnosed with PTSD, the person must have been exposed to a traumatic event in which the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death, serious injury, or a threat to the physical integrity of self or others (American Psychiatric Association [DSM-IV-TR], 2000). The person’s response to the experience must involve intense fear, helplessness, or horror. The victim must persistently re-experience the traumatic event through visual images, thoughts, dreams, or mental recreation of the event. The individual must avoid stimuli associated with the trauma and have persistent symptoms of increased arousal. Finally, the

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duration of the disturbance must be more than one month (American Psychiatric Association [DSM-IV-TR], 2000).

Posttraumatic stress disorder is a serious anxiety disorder with a lifetime prevalence of approximately 6.8% in the United States and a 12 month prevalence of 3.8%. 50-60% of all North Americans experience a traumatic stress in their lifetimes, and 15% of these traumatically stressed individuals will subsequently develop PTSD (Adamec, Muir, Grimes, & Pearcey, 2007). Furthermore, approximately 30% of patients will still be suffering from PTSD at least ten years after the trauma (Langevin, De Salles, Kosoyan, & Krahl, 2010). This finding is highly troubling because research has shown that if PTSD symptoms have not been resolved within 6 years, the symptoms are highly likely to remain chronic (Cantor, 2005).

The symptoms of PTSD reflect stress-induced changes in neurobiological systems and/or an inadequate adaptation of neurobiological systems to exposure to severe stressors. However, it is not clear which specific neurological systems, neurotransmitters, or abnormal brain structures cause PTSD. Neurobiological systems that have been implicated in the

pathophysiology of PTSD include the hypothalamic-pituitary-adrenal (HPA) axis, and various neurotransmitters and neuropeptides that comprise a network of brain regions that regulate fear and stress responses. These include the prefrontal cortex, hippocampus, amygdala, and brainstem nuclei (Heim & Nemeroff, 2009). The neurocircuitry that has been scrutinized in PTSD patients has been the HPA axis. The HPA axis is an organism's major neuroendocrine stress response system which affects metabolism, immune function, and the brain, adjusting physiological functions and behavior to stress (Heim & Nemeroff, 2009). The HPA axis' sensitivity is increased after a traumatic event by a strong negative feedback of cortisol which is due to the highly increased sensitivity of cortisol receptors (Heim & Nemeroff, 2009). Another mediator of HPA axis activity is norepinephrine. Norepinephrine (NE) is produced by the adrenal medulla through sympathetic stimulation and the local effects of cortisol, and provides positive feedback to the pituitary gland maintaining the stress response and further stimulating the HPA axis (Vermetten & Bremner, 2002). Norepinephrine is also thought to play a role in the

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encoding of memories (Vermetten & Bremner, 2002).

The present study will focus primarily on the development and course of PTSD as it relates to the secretion of NE. Because of its multiple roles in regulating arousal and autonomic stress responses through its interaction with the HPA axis, as well promoting the encoding of emotional memories, NE has been a central candidate in studying the pathophysiology of PTSD (Heim & Nemeroff, 2009). NE is one of the principal mediators of the central nervous system (CNS) and autonomic stress responses. The majority of CNS NE is derived from neurons of the locus ceruleus (LC) that project to various brain regions involved in the stress response, including the prefrontal cortex, amygdala, hippocampus, hypothalamus, periaqueductal grey, and thalamus (Heim & Nemeroff, 2009). Accordingly, increased urinary excretion of NE and epinephrine has been documented in combat veterans, abused women, and children with PTSD (Strawn & Geraciotti, 2008).

Many approaches to the treatment of PTSD have been taken, in animal models as well as in humans. While the diagnostic criteria for PTSD have only existed since 1980, hundreds of clinical trials

have sought to identify methods of ameliorating its distressing symptoms (Cukor, Spitalnick, Difede, Rizzo, & Rothbaum, 2009). Current treatments for PTSD include psychological interventions including social and family based therapy, behavioral treatments, imagery-based treatments, therapies focusing on distress tolerance, "power" therapies, and technological-based treatments (Cukor et al., 2009). Although there have been significant advances in the treatment of PTSD, treatment failures persist.

Another form of treatment is pharmacological treatment, and is the focus of recent research pertaining to PTSD treatment and prevention. Over the past decade, many compounds have been tested as treatments for PTSD. Corticosteroids, beta-adrenergic antagonists, and opiate analgesics have been shown experimentally to reduce hormonally enhanced memories and fear conditioning (Cohen, Kozlovsky, Matar, Kaplan, & Zohar, 2010). Propranolol, a beta-adrenergic antagonist, has received great attention, and is hypothesized to decrease the consolidation of stressful memories due to its inhibitory effects on NE receptors, and indirectly the HPA axis.

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The focus of the present study is on the efficacy of propranolol as a preventative treatment for the development of PTSD following a traumatic experience. Propranolol is a non-selective beta-adrenergic antagonist that binds to peripheral and central  $\beta$ -adrenergic receptors and readily crosses the blood-brain barrier (Vaiva et al., 2003). Thus, propranolol may be used to block  $\beta$ -noradrenergic receptors and the consolidation of the fear memory.

Attempts to mitigate PTSD symptoms with post stressor block of  $\beta$ -noradrenergic receptors by treatment with propranolol have mixed results, but there is evidence that propranolol reduces PTSD symptom severity (Pitman et al., 2002; Reist et al., 2001; Vaiva et al., 2003). Propranolol given within 6 hours of a traumatic event for 10 days was superior to a placebo for reducing PTSD symptoms 1 month after trauma (Pitman et al., 2002). Vaiva and colleagues studied motor-vehicle accident survivors and the effects of propranolol on the development of PTSD. Vaiva et al. found that in comparison to eight traumatized patients who did not receive propranolol, treatment with propranolol was superior. Only one in 11 treated patients developed PTSD two months after the trauma, whereas PTSD developed in three of

the eight untreated patients (Vaiva et al., 2003). Although some research has found propranolol ineffective in treating PTSD symptoms (Cohen et al., 2011), the majority of evidence has found that the administration of propranolol shortly after (or before) exposure to psychological trauma reduces PTSD symptom severity and reactivity to reminders of the traumatic event (Heim & Nemeroff, 2009).

This study attempts to determine the effectiveness of propranolol as a preventative treatment for PTSD symptoms. In order to accomplish this, an animal model of PTSD was influenced, and the treatment tested in the animal population. To date, little research has been completed in an animal model.

The criteria for inducing PTSD in an animal model should include the same criteria as a diagnosis of PTSD by the DSM-IV-TR. There should be the application of direct physical stressors in conjunction with exogenous stimuli that closely mimic those seen in nature. Furthermore, the stressors should create a fear for one's life. When these criteria are followed, stressed rats tend to show PTSD-like behavior such as increased immobility, decreased grooming and rearing, decreased exploratory

behavior and decreased food consumption (Kesner et al., 2009).

The present study strives to develop an animal model of PTSD in rats, and then attempt to evaluate the effects of propranolol on PTSD symptoms. Rats are exposed to inescapable shocks paired with the scent of bobcat urine in order to create a trauma eliciting PTSD. Rat behavior (levels of anxiety, burying behavior, and freezing behavior) is observed pre- and post-stress to indicate whether rat behavior has changed in response to the traumatic experience. Given that rodent behavior changes, propranolol is used as a treatment for PTSD symptoms. All in all, this study addresses two guiding questions for the research: 1) Can an accurate animal model for PTSD be developed? and 2) Does propranolol, a  $\beta$ -noradrenergic antagonist, reduce PTSD symptoms in a rat model?

My hypotheses are that (1) rat behavior will be altered in response to a traumatic experience, and subsequently that symptoms similar to PTSD behavior can be observed in an animal model and (2) propranolol will effectively reduce the severity of PTSD symptoms.

## 2. Method

All procedures were carried out under strict compliance with ethical principles and guidelines of the NIH Guide for the Care and Use of Laboratory Animals. All treatment and testing procedures were approved by the Institutional Animal Care and Use Committee of Regis University in Denver, Colorado.

### 2.1. Animals

Adult, female Sprague-Dawley rats were used throughout the study. The animals were housed singly or in pairs in a cage with a width of 10 inches, a length of 18.5 inches, and a height of 8 inches. The conditions in the animal facility were controlled at 72 °F. The animals were held in an environment with a twelve hour light – twelve hour dark cycle (06:00–18:00 light). All animals had food and water available *ad libitum*. The cage bedding was changed every 2-3 days.

### 2.2. Experimental design

The study consisted of two main experiments, each assessing the effectiveness of propranolol as a treatment for post-traumatic stress disorder in an animal model but

differing in the behaviors assessed. The independent variables were the stress and treatment conditions. The stress conditions were either stress exposure or no stress exposure. The treatment conditions were either no treatment, a saline injection, or a propranolol injection. The dependent variables were the rats' ball burying behavior, elevated plus maze performance, and freezing behavior.

### ***2.2.1 Experiment 1***

Experiment 1 consisted of two parts. Part 1 intended to develop an animal model of PTSD. Rats were randomly assigned to one of two conditions, an inescapable stressor condition or a control condition. In the inescapable stressor condition, each rat was exposed to moderate shocks (shocks of 0.5 second duration and 1.5 mA intensity) occurring at 30 second variable intervals for 10 minutes, combined with a predator stress, bobcat urine. All stress exposures occurred in a standard operant chamber. During the stress exposure period, the rat was exposed to a novel object, a soft-flight golf ball. The control animals were exposed to fresh, unsoiled cedar chips and received no shock, but were exposed to the novel object. Neither the experimental rats nor the control rats received any treatment

after the stressors during Part 1 of the experiment.

Part 2 of Experiment 1, followed the same protocol. However, after the stress exposure period, the animals were immediately injected with a 10 mg/kg dose of propranolol intraperitoneally.

To evaluate whether the rats developed PTSD-like behavior, two assessment strategies were used in Part 1 of Experiment 1, and all assessment was completed at 7 days as well as 28 days post stress exposure. First, the novel object, the soft-flight golf ball, was placed back with the rat, in its normal living conditions, for fifteen minutes, to assess the rat's burying behavior. Rats bury a novel object when it has been paired with a traumatic experience (Harvey et al., 2006). The second assessment tool was an elevated plus maze, which was used to assess anxiety. The dimensions of the maze were 64.5 inches by 64.5 inches. Each arm was 30 inches in length.

### ***2.2.2. Lever pressing training protocol***

Prior to the start of Experiment 2, the animals were trained to press a lever in the operant chamber for a sugar pellet

reward. The training process shaped the rats' behavior. Each rat was placed in an operant chamber and shaped to stay the one side of the chamber with the levers, then to rear up on that side of the chamber, and eventually to press the right or left lever. When a rat performed a desired behavior, it was rewarded with a sugar pellet reward.

Lever pressing behavior was reinforced until the animal was able to receive at least 50 sugar pellets within 20 minutes; first at a ratio of one lever press to one sugar pellet, and then at a ratio of 5 lever presses to one sugar pellet. To achieve this level of conditioning, four successful reinforcement trials were utilized. Each animal was placed in an operant chamber and allowed to receive 50 sugar pellets for itself via pressing either the left or right lever. Once this mark had been reached in two successive trials, the animal was removed from the chamber. After two trials of training on the one lever press to one sugar pellet fixed ratio, the animal was trained to press the lever five times to receive one sugar pellet. Each training session on this five lever presses to one sugar pellet fixed ratio lasted until the animal received at least 50 sugar pellets. Two 5:1 fixed ratio training sessions took place.

### *2.2.3 Experiment 2*

Experiment 2 consisted of three parts. All three parts of this study were based on the rats' ability to press a lever to receive a 45 mg sugar pellet. Before Part 1 of the study began, the rats' rate of lever pressing for a sugar pellet reward (on a 5:1 fixed ratio) was assessed and recorded as a control measure for lever pressing behavior.

Part 1 of Experiment 2 further focused on developing an animal model for PTSD, but used freezing behavior, rather than burying behavior or anxiety, as the predicative factor of PTSD. After being trained to press the lever in an operant chamber, the rats were placed into the operant chamber and exposed to inescapable, moderate shocks (shocks of 0.5 second duration and 1.5 mA intensity) occurring at 30 second variable intervals for 10 minutes, as well as a predator stress, bobcat urine. A bright light was paired with each shock. During this session the rats were still able to press the lever to receive a sugar pellet (at a 1-to-1 fixed ratio). At 7, 14, and 21 days, the rate of lever pressing for each rat from Part 1 of Experiment 2 was assessed in the presence of the bright light, to assess the degree of freezing each rat expressed.

Part 2 of Experiment 2 followed the same protocol as Part 1 of Experiment 2. However, a 10 mg/kg intraperitoneal injection of propranolol was given immediately following the stress exposure period. The assessment strategy for Part 2 of Experiment 2 was identical to that of Part 1 of Experiment 2.

### **2.3. Chemicals**

Propranolol (15 mg/kg) was dissolved in saline and administered via intraperitoneal injection. Controls received an equivalent volume of 0.9% saline solution in the same manner, controlling the potentially stressful effects of an intraperitoneal injection. The drug or vehicle solutions were freshly prepared and injected at the same time of day in a volume of 1 ml/kg body weight.

### **2.4. Behavioral measurements**

Over the course of the two studies, an elevated plus maze and lever press rate comparisons were used to assess anxiety and freezing behavior, which are indicative of PTSD-like symptoms. All behavioral measurements were recorded by the experimenter at the time of assessment.

#### **2.4.1. The elevated plus-maze**

In Experiment 1, the rats were assessed on the elevated plus maze (EPM). The EPM creates a conflict situation between the exploratory drive of rodents and their aversion to open spaces (Pellow et al., 1985). The maze consists of two open arms and two closed arms. The maze forms a "+" with the open arms and closed arms lying along their respective axes. The maze was raised 24 inches above the floor. The rat was placed in the center of the apparatus facing an open arm and allowed to explore the maze for 5 minutes under constant observation. An arm entry was considered when all four paws crossed from one arm and into the other. The amount of time spent in the open arm versus the amount of time spent in the closed arm was recorded. The more time the animal spent in the closed arm, the higher degree of anxiety the animal was believed to have. An image of an EPM is displayed in Figure 1.

To assess the degree of anxiety exhibited by the rat, the rats' anxiety ratios were obtained.

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The higher the anxiety ratio, the greater the amount of anxiety the rat expresses.

### 2.4.2. Ball burying behavior

The frequency of ball burying is predicative of PTSD in an animal model. Although burying is a rare behavior in wild rats, it is thought to represent the symptoms of PTSD when it follows a stress exposure period (Mikics et al., 2008). The animals were exposed to the soft-flight tennis ball for a 15 minute period at 7 days post stress as well as 28 days post stress. The amount of time the animal spent burying the ball, exploring the ball (sniffing, biting, or grabbing the ball), and the amount of time spent ignoring the ball was observed and recorded by a single examiner.

### 2.4.3. Rate of lever pressing

The two previous methods of assessment (used in Experiment 1) did not measure the degree of freezing which is a hallmark trait of PTSD in an animal model. In Experiment 2, the degree of freezing was assessed by comparing the pre-stress rate of lever pressing with the rate of lever pressing 7, 14, and 21 days following the traumatic experience. A suppression ratio was

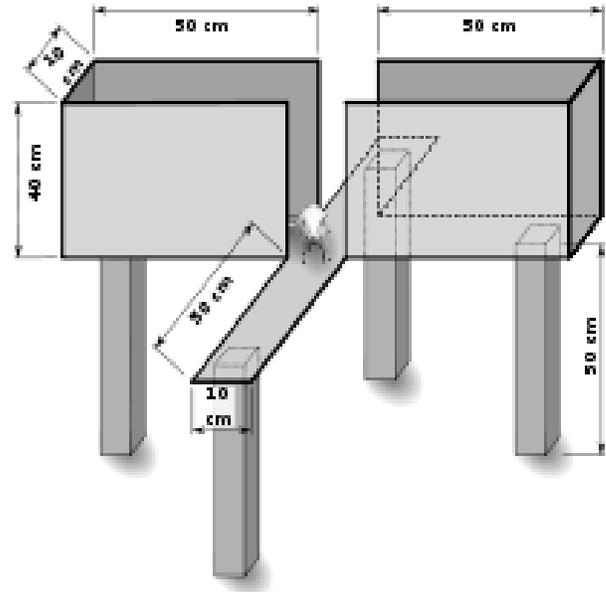


Figure 1. – Detailed image of an elevated plus maze.

used to assess the rate of lever pressing post trauma in order to account for the press rate when the light was on as well as when the light was off.

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The suppression ratio is inversely proportional to the degree of suppression. As the suppression ratio decreases, the amount of suppression increases.

The greater the difference in these measures pre and post stress, the higher degree of freezing the animal has had. The control animals were assessed at the time of stress, although they themselves were not stressed, 7, 14, and 21 days after the stress. This provides an indication of the reduction of lever pressing over time.

### 3. Results

#### 3.1. Experiment 1 - Effect of stress, propranolol, and time on anxiety-like behavior and ball burying behavior.

Experiment 1 assessed the degree of anxiety exhibited by the rats as well as the degree of avoidant behavior exhibited by the rat.

The anxiety ratios were analyzed for effects of stress (stress or no stress), treatment (immediate administration of a propranolol injection or a saline injection), and time (7 days post trauma or 28 days post trauma). A univariate ANOVA revealed that there was no significant effect of stress on anxiety,  $F(1,27) < 1$ .

However, the treatment condition did appear to show an effect. The rats who received the saline injection had a mean anxiety

ratio of  $.819 \pm .241$  while the rats who received the propranolol injection had a mean anxiety ratio of  $.692 \pm .344$ . Some rats received propranolol and were observed 7 days post stress; the mean anxiety ratio of this group was  $.910 \pm .103$ . Others were observed 28 days post stress; the mean anxiety ratio of this group was  $.540 \pm .375$ . There was a main effect of treatment on anxiety,  $F(1,27) = 4.85, p = .036, \eta p^2 = .152$  (Figure 2).

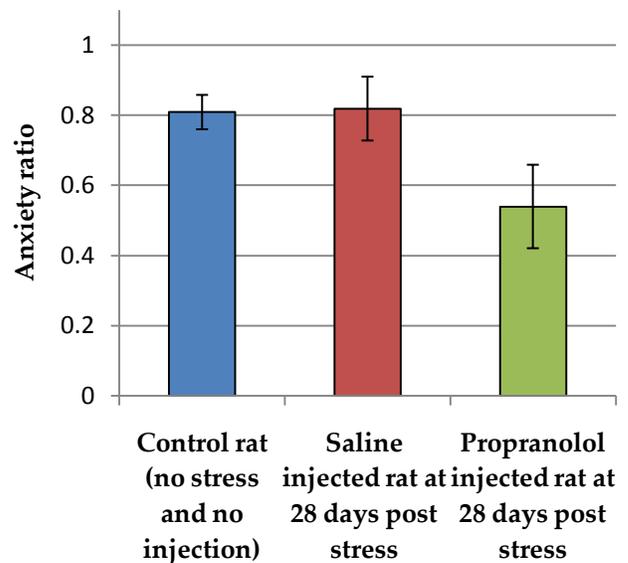


Figure 2. – This figure illustrates the mean anxiety ratios of the control group, saline group, and propranolol group 28 days after the stress trial. The difference between the control rats and the rats who received the stress with no treatment was insignificant 28 days after the stress trial. However, the administration of a propranolol injection following the stress trial significantly reduced the anxiety ratio expressed by the rats  $F(1,27) = 4.85, p = .036$ .

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Time also had a significant effect on the rats' anxiety. The mean anxiety ratio of rats assessed 7 days post stress was  $.910 \pm .103$ . The mean anxiety ratio of rats assessed 28 days post stress was  $.700 \pm .306$ . There was also a main effect of time on anxiety,  $F(1,27) = 8.52, p = .007, \eta^2 = .240$  (Figure 3).

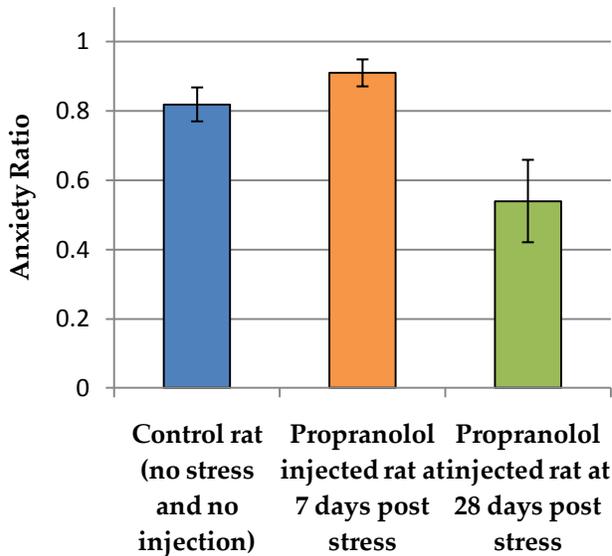


Figure 3. – This figure focuses on the effectiveness of propranolol over time. The effect of time on anxiety ratio is significant in that it causes the anxiety ratio to increase, even when propranolol was administered as a treatment, at seven days post stress but decrease beyond the level of pre-morbid functioning at 28 days post stress (when treated with propranolol,  $F(1,27) = 8.52, p = .007$ ).

Experiment 1 also assessed ball burying behavior by the rats as a measure of avoidant behavior. Only four of 31 rats (28 of which were stressed) exhibited any degree of ball burying behavior. There were no effects of stress ( $F(1,27) < 1$ ), treatment ( $F(1,27) = 2.493, p = .126$ ), or time ( $F(1,27) < 1$ ) on ball burying behavior.

### 3.2. Experiment 2 - Effect of propranolol and time delay until assessment on post-stress freezing behavior

Experiment 2 aimed to evaluate the rat model of PTSD used in the present study by assessing freezing behavior as a result of the stress induced. In order to initially test freezing behavior due to the induced stress, a baseline rate of lever pressing was observed pre-stress and then each rat's post stress lever press rate was observed 7, 14, or 21 days after the stress was administered. A *t*-test was conducted on baseline lever press rate and post stress lever press rate. The post-test rate of lever pressing was significantly lower than the baseline rate of bar pressing behavior ( $t(32) = 5.977, p < .001$ ).

Upon establishing that the animal model of PTSD significantly affected the rats' bar press rates, a

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univariate ANOVA was conducted to determine the effects of the treatment condition and time condition on press rate behavior. The baseline press rate was covaried in order to eliminate any effects that the rat's baseline press rates may have on the analyses.

Propranolol did not have a significant effect on lever press rate as indicated by the rats' suppression ratios. The rats that were given a saline injection had a mean suppression ratio of  $.545 \pm .110$ . The rats given a propranolol injection had a mean suppression ratio of  $.590 \pm .121$ . The effect of propranolol on lever press rate was insignificant,  $F(2,23) = 1.99, p = .158, \eta p^2 = .148$ .

The effect of time did significantly affect the rats' lever press rate as indicated by their suppression ratios. The rats' mean suppression ratio when observed 7 days after stress was  $.529 \pm .101$ . The rats' mean suppression ratio when observed 14 days after stress was  $.642 \pm .107$ . The rats' mean suppression ratio when observed 21 days after stress was  $.495 \pm .088$ . The amount of time elapsed between stress and observation was significant,  $F(2,23) = , p = .002, \eta p^2 = .409$  (Figure 4).

A pairwise comparison of the time data indicates that the mean suppression ratio of rats observed at

week one is significantly lower than the mean suppression ratio of rats observed at week two,  $p = .004$ , and that the mean suppression ratio of rats observed at week three is significantly lower than the mean suppression ratio of rats observed at week two,  $p = .001$ . The suppression ratios of rats observed at weeks one and three were not significantly different.

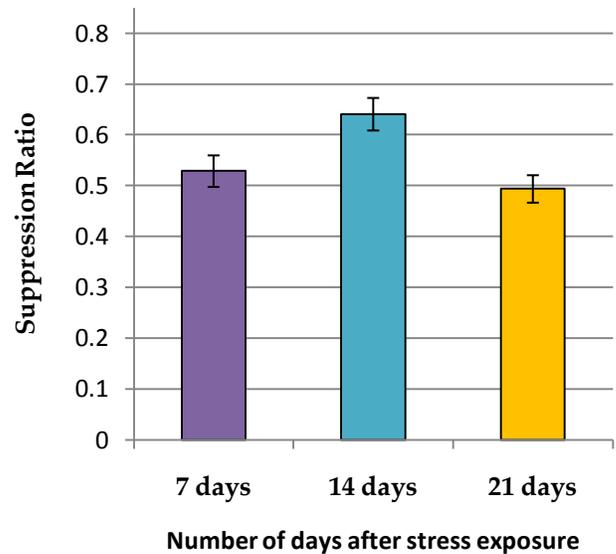


Figure 4. – This figure focuses on the effect of time on suppression ratio as a measure of freezing behavior,  $F(1,23) = 7.962, p = .002$ . As time increased since the stressor, the degree of suppression measured had increased at the 14 day mark but then decreased at the 21 day mark.

## 4. Discussion

### 4.1. Discussion of results found in Experiment 1

The main findings from experiment 1 were threefold: 1) there is no effect of the stressful experience used in this experiment on the rats' anxiety ratios, 2) propranolol did effectively reduce the rats' amount of anxiety 28 days after the stress experience, and 3) the time course data suggests that the rats' anxiety ratio increased at 7 days post-stress but had normalized back to the control measure by 28 days post stress.

The finding that the stressful experience does not affect the rats' levels of anxiety 28 days post trauma (as indicated by the EPM data) suggests that either the stress experience used to elicit PTSD-like behavior did not significantly affect the rats' level of anxiety or potentially that laboratory rats are in a perpetual state of anxiety and stress. An argument can be made that the present stress protocol did not alter anxiety levels or elicit PTSD-like symptoms because of the procedure of the present study. Support for this claim comes from the lack of burying behavior by the rats in response to the stress and treatment. However, Langevin et al.

(2010) claims that burying behavior is a rare behavior in wild rats. Burying behavior would have suggested that the rat wanted to flee the object associated with the stress experience. If the stress procedure was not sound, the rats may have paired the memory of the stress experience with the operant chamber rather than the novel object, explaining why burying behavior did not occur. Another plausible explanation is that the rats simply did not know how to bury.

The rats may not have exhibited changes in anxiety ratios because they were already anxious. The continual handling, transportation, and movement of the laboratory rats, in addition to their unnatural housing environment, may lead the animals to be in a constant state of anxiety. Data presented in Experiment 1 supports both of these theories.

In order to confirm one of these theories, further experimentation must be completed. First, it would be useful to use the current procedure and collect the same data again, but to also collect data at 7 days post-stress for the anxiety ratio of rats that were given a saline injection. It would also be beneficial to calculate the anxiety ratios and observe the burying behavior of rats (in the same control

and experimental groups) when stressed with a different stress protocol. A time dependent sensitization stress paradigm using restraint and forced swimming have also been effective in eliciting PTSD in an animal model (Harvey et al., 2006).

Another significant finding is that propranolol effectively reduces rats' level of anxiety 28 days post-stress. This finding supports that propranolol effectively reduces anxiety (Pitman et al., 2002; Vaiva et al., 2003). The claim that the stress experience does alter the rats' level of anxiety because it causes the rat to lose all recollection of emotions associated with the experience seems to be supported.

Propranolol does not show this same effect 7 days post-stress. At 7 days post-stress, the mean anxiety ratio is increased from the control measure (the anxiety ratio of non-stressed rats) to 0.910. Although the anxiety ratio has increased, propranolol was not proven effective at 7 days post stress for decreasing the rats' anxiety ratio due to insufficient information. The anxiety ratio of saline injected rats 7 days post stress was not observed. Thus, propranolol may have an effect on rats' anxiety ratios one week after stress, but if so, the effect is not great because the anxiety ratio still

increased significantly from the control. Propranolol's inability to reduce anxiety 7 day post trauma supports Cohen et al.'s (2011) claims that propranolol is ineffective in preventing PTSD.

The data from Experiment 1 also suggests that there is a time course associated with the effectiveness of propranolol or the presentation of PTSD-like symptoms. The data concerning time course shows that propranolol has greater effectiveness at 28 days, than at 7 days, post stress. Therefore, the data indirectly suggests that the rats' anxiety level increases 7 days post stress, but then normalizes again by 28 days post stress. The rats' mean anxiety ratio increased at 7 days post stress despite the propranolol treatment, and then normalized at 28 days post stress. These findings support a time course to be associated with PTSD symptoms, and that PTSD symptoms do not necessarily develop immediately following the trauma.

### *4.2. Discussion of results found in Experiment 1*

Experiment 2 yielded two findings worth further discussion: 1) propranolol did not significantly affect freezing behavior and 2) time

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after stress influences the degree of freezing behavior in rats.

When propranolol treated rats' freezing behavior (as indicated by the suppression ratio of lever pressing with the light on) was compared to the saline treated rats' freezing behavior, there was not a significant effect. This may be explained in two ways. One explanation is that the propranolol administration did not effectively treat the symptoms elicited by the stress experience. For instance, one dose of propranolol immediately following the stress may not have a great enough effect on the rat. In human trials, a series of doses must be administered to see an effect on PTSD symptoms (Vaiva et al., 2003). Likewise, the one dose of 15mg/kg may not have significantly affected the rats' behaviors or symptoms. The other issue may have arisen in the process of pairing the stressful experience with the novel object. It may be that the rat did not pair the stressful event with the novel object, but the operant chamber itself.

The data collected from Experiment 2, like Experiment 1's data, suggest a time course for PTSD-like symptoms. The mean suppression ratio of rats observed at 14 days post stress were greater than the suppression ratios of the rats observed at 7 days post stress, but

the mean suppression ratio of rats observed 21 days after the stress were lower than the suppression ratios measured at 7 days post stress. Thus, the degree of suppression began to increase again between 14 and 21 days post stress. Using freezing behavior as the determining factor of PTSD in an animal model, an animal model of PTSD may be developing by 21 days post stress, but does not begin to develop before. This data supports the data from Experiment 1, indicating that PTSD symptoms do not develop immediately after the stress.

## 5. General Discussion

Based on the results of the two experiments conducted in this study, neither of the two hypotheses presented at the beginning of the study were supported. The stress experience did not affect the rats' ball burying behavior or anxiety level 28 days post trauma, and although propranolol did reduce anxiety, it did not significantly affect ball burying or freezing behaviors, which were also used as measures for PTSD symptoms.

Despite rejection of the hypotheses, the present study does prove useful for future PTSD research. The pre and post stress

lever press rates and suppression ratios suggest that an animal version of PTSD was elicited in the rats. Likewise, if future research indicates that the lack of anxiety level increases at 7 days post stress, then it may be concluded that the stressful experience did in fact resemble a trauma that could elicit PTSD-like symptoms. The present protocol for eliciting PTSD-like symptoms may be slightly altered to truly determine if the present stress protocol does produce PTSD-like symptoms in rats and if propranolol effectively prevents such symptoms. Additionally, this data indicates that propranolol is effective for treating anxiety. The data also provides support for a delayed development of PTSD symptoms.

The findings from this study suggest that PTSD symptoms do not develop immediately following the trauma, but take time to develop. In this rat model, PTSD symptoms do not begin to exhibit themselves until the third week after the stress experience. Evidently, posttraumatic stress disorder does exhibit itself in different patterns. Different individuals may respond to a single trauma very differently. Individuals may also differ in their presentation of the PTSD symptoms. Symptoms may appear immediately after the trauma or months or years later

(Cantor, 2005). This study indicates that the time course for a rat to exhibit PTSD-like symptoms is approximately 3 weeks. Hopefully this study provides insight to future studies regarding the testing of PTSD and potential treatments of the disorder in the animal model.

In conclusion, despite finding no significance of the effects of propranolol, this study was successful in unexpected respects and contributes to the neuroscience and PTSD research fields.

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**The Afterword:**  
**One treatment, many implications, more questions...**

“Everybody says we're all so different  
But everybody knows we're all the same  
We're all trying to find a pill to numb the pain  
Something's got to change”

*~ Josh Wilson, Something's Got to Change*

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*The effects of propranolol, a non-selective  $\beta$ -adrenergic antagonist, on rat behavior in an animal model of posttraumatic stress disorder* is the foundation for this thesis and provides new research to the field of neuroscience and PTSD literature. Through this study, the effects of propranolol on a rat version of PTSD, which was influenced through a stress protocol adapted from previous fear conditioning and PTSD studies, were tested. Propranolol did not effectively decrease all PTSD symptoms in this study, as I had expected, but I did find that a single 15 mg/kg dose of propranolol administered immediately after stress significantly reduced the rats' freezing behavior 28 days after administration. I also found that the PTSD-like symptoms that the rats experienced had a distinct time course. Furthermore, this research has helped me generate more ideas for potential studies concerning the development of pharmacological treatments for PTSD. Ultimately, this study led me to insights regarding PTSD, propranolol, and PTSD research.

Although the research completed, and presented in this thesis led to positive, yet unexpected, results, I realize that many ethical questions arise from this research as well. The present study did not support the hypotheses stated at the onset of the experiments or lead to any truly extraordinary findings in regards to a treatment for posttraumatic stress disorder (PTSD). It did however,

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subject animals to psychological stress. Although researchers design experiments to yield results consistent with their hypotheses, this does not always occur. My study is not the only study that has ever failed to support its hypotheses, and it definitely will not be the last. The stresses of experimentation, however, are present across all research and are consistently impressed upon the research subjects or participants. Thus, the question arises, should scientific research which causes any element of harm be tolerated? This complex question tends to polarize people. The views concerning scientific research, and each of its subtypes, range from fully condemning research to entirely supporting it as the most beneficial tool for furthering knowledge about the world. The use of animals as research subjects is a clear example of this polarization, and is another ethical concern brought about by my study. Why should one complete research on animals rather than humans? Is an animal's life less valuable than the life of a person?

In addition to the questions directly surrounding my research, questions surround the search for a treatment for PTSD. The overarching question is whether or not individuals suffering from PTSD should be provided a pharmacological treatment to prevent or reduce their symptoms. The initial response to this question may seem simple, but when the side effects of the

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treatment(s) are taken into consideration, the answer becomes more convoluted. To treat PTSD, the memory of the trauma or the relationship one has with that memory must be treated. Most pharmacological treatments aim either to eliminate the memory completely or to blunt the emotions associated with the memory. Ethical questions arise concerning the value of one's memory, the value of one's emotions. After exploring these questions, one must also question how a pharmacological treatment may be implemented and the greater effects of a PTSD treatment on society.

Questions like these often go overlooked in the scientific community, but regardless, it is important to investigate such ethical questions. Although it would be an amazing scientific feat to discover a treatment, one cannot ignore the ethical questions surrounding PTSD treatment research simply because of the scientific interest. It is also important to think about each ethical question individually, and not simply agree with the common answers to the ethical questions.

Before I begin exploring the overarching question of whether or not a treatment of PTSD should be made available, I must address the ethical concerns of scientific research. In the following section I will outline the current stance of

the scientific community on scientific research that uses humans as research participants and that uses animals as research subjects.

**I. Current views of scientific research using humans as research participants and animals as research subjects**

The general view of the scientific community is that scientific research is justifiable with the participant consent to the investigation as long as no harm is deliberately imparted upon the participant. Immanuel Kant states that “a human being, and in general every rational being, does exist as an end in himself, not merely as a means to be used by this or that will as it pleases” (Sandel, 2007). I completely agree with this Kantian philosophy, and so does the scientific community. Although scientific research may not always produce the results that the researcher(s) believed it would, the benefits of scientific research will continue to outweigh the costs as long as the participants’ individual rights are respected and the ethical guidelines outlined above are upheld. If any form of research were proposed in which people were forced to participate in a study or the study infringed upon the participant’s rights, the research would not be allowed to occur. Each person should be treated equally, and guaranteed his or

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her rights. In order to guarantee that each person is treated as an end in himself, ethical principles have been developed to guide scientific research.

Three primary principles must be upheld in scientific research that uses humans as research participants. The first principle is *respect for persons*. This principle emphasizes the inherent dignity and worth of each person. The principle requires science to respect individuals and their autonomy; it means not treating people simply as a means to an end, but encouraging their right to self-determination and the right to make choices, to hold views, and to take actions based on personal values and beliefs. Based on this principle, one should always “act in such a way that you treat humanity...always at the same time as an end, never merely as a means” (Sandel, 2007). The *respect for persons* principle emphasizes the responsibility individuals have for their own lives. The second principle has to do with *maximizing benefits while minimizing harms*. To maximize benefits one would help others and act in their best interests while creating the greatest wealth of new knowledge. Meanwhile, minimizing harms obligates others to minimize the amount of harm intentionally inflicted on the participant. The third principle relates to *giving each person his or her due*. This dictates that each person should qualify for equal treatment because each person is equally

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human. All resources, risks, and costs should be equally available (NWABR, 1999).

In addition to these three principles, more pointed guidelines must also be followed. The American Psychological Association has outlined ten general principles governing the conduct of research with human participants. Among these principles are: gaining institutional approval for the research at hand (if necessary), gaining informed consent to research from the research subject, gaining informed consent for recording voices and images during research, ensuring protection of subordinate research participants (students, patients, clients, etc.) from adverse consequences of declining or withdrawing from participation, dispensing information only with informed consent and for a legitimate reason, offering reasonable inducements for research participation, minimizing deception in research, providing a debriefing session for the research participant(s), and caring for all animals involved in research in a humane manner (Elmes, Kantowitz, & Roediger III, 2006). Although these ethical guidelines are expansive, they are necessary to allow for the pursuit of knowledge through scientific research in an ethical manner. These principles are intended to protect the welfare of research participants, and they can be

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summarized by noting that the experimenter has an obligation to minimize harm to the participant while treating him or her with respect and seeking to maximize the benefits that may be gained from the research.

As long as the aforementioned ethical guidelines are upheld, scientific research and the resulting knowledge is not only ethical, but it is necessary. Science is the only avenue of learning for certain disorders. For instance, the etiology and treatment of psychological disorders cannot be understood without studying the individuals with the disorder or inducing such a disorder in an animal subject or human participant in order to test potential treatments. Even though some research has already been conducted on PTSD, very little is known about the disorder. While it is known that the hypothalamic-pituitary-adrenal (HPA axis), the hippocampus, the amygdala, the prefrontal cortex, as well as six neurotransmitters and neuropeptides are implicated in PTSD, it is not clear which abnormalities within the CNS actually lead to the development of PTSD symptoms. Thus, there is a tremendous need for more research on the neurological abnormalities that underlie PTSD. Perhaps if a person can understand the neurochemistry of PTSD he or she can find a treatment for the disorder. Without the ability to complete scientific research, treatments for

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psychological disorders like PTSD would never be developed. As long as person's rights are respected, scientific research that uses humans as participants is encouraged.

The scientific community does not hold quite as stringent views on animal research. Although a better understanding of the neurobiology of PTSD may be obtained through the dissection of human brains that have experienced PTSD, and eliciting PTSD in humans rather than animals would lead to understand PTSD as it affects the human brain, these research techniques violate the ethical guidelines of human research. However, the scientific community is comfortable with using these same research techniques in animal models.

Animals may be used for certain types of research that humans cannot because of the need for better scientific understanding of diseases and disorders as well as the logic that animals do not have the same moral rights as humans. Every effort should be made to do what is best for the individual and society as a whole. The pursuit of a treatment for PTSD, and any other psychological disorder, would allow for the individual to return to his or her premorbid level of functioning and a degree of suffering would be removed from the world. Animal research may be a way to obtain this objective. Cohen (1986) explains that animals are incapable of moral agency and therefore lack moral rights.

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Rights only arise among beings that can actually make moral claims against one another. Animals do not have the capability of moral judgment, and therefore, do not have any rights (Cohen, 1986). Based on the knowledge to be gained from animal research coupled with the belief that animals do not have moral agency, the scientific community believes that animals should be appropriately used to advance biomedical research (Mappes & Degrazia, 2006). The scientific community allows animal research in the pursuit of furthering scientific knowledge.

Although researchers are able to use animals as research subjects, they are not free to treat animals in any way that they see fit. Animals certainly suffer, and should not be made to suffer needlessly. It is accepted that animals do not have a moral status comparable to that of humans. This is evident through our willingness to set a mouse trap or prepare a boiling pot of water for a lobster dinner. However, it is also generally agreed upon that animals have certain liberties. The biomedical and animal protection communities both agree on the following: the use of animals in biomedical research raises ethical questions, sentient animals deserve moral protection, animals are capable of having a wide variety of aversive mental states (including pain, distress, and suffering), and animals' overall well-being deserves protection (Hettinger, 1989). On the other

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hand, these communities also agree that promoting human health is extremely important and that there are some morally significant differences between humans and other animals (Hettinger, 1989). From these beliefs, it is accepted that animal research is justified only when the ethical guidelines for animal research are followed.

The Council for International Organizations of Medical Sciences (CIOMS) assumes that the moral status of animals does not preclude the need for animal use in research. At the same time, CIOMS asserts that researchers have certain responsibilities to minimize the animal's pain, distress, and discomfort and must use alternatives to animal research whenever possible (Mappes & Degrazia, 2006). In accordance with the CIOMS's view, Bear et al. (2007) gives three main responsibilities that neuroscientists must uphold when conducting neuroscience research with animal subjects.

1. Animals should only be used for experiments that promise to increase knowledge of human systems or diseases affecting those systems. In other words, the benefits of the experiment must outweigh the costs. If animals must be sacrificed or harmed, the experiment must be in the pursuit of greater knowledge.

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2. All possible steps must be taken to minimize any pain or distress the animal may experience.
3. The researcher must consider all possible alternatives to the use of animals as research subjects.

If these three responsibilities are upheld, animals are acceptable research subjects. The general assumption among the research community is that it is unethical to use animals profusely or for commonplace research, but that “it is immoral not to wisely use all the resources that nature has provided, including animals, to gain an understanding of how the brain functions in health and disease” (Bear et al., 2007). Animals may, and should, be ethically used in scientific research so long as such research eventually leads to an overall greater quality of life.

In summary, scientific research is not only accepted but also encouraged as long as the previously outlined ethical guidelines are upheld for human research participants and animal research subjects. For the research that cannot be completed with human participants, animals are the avenue in which this knowledge may be acquired. Although it would be ideal to inflict no harm in the pursuit of knowledge, this is not always possible. Every benefit has a cost

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associated with it. The scientific community has decided that the benefit of developing cures for various diseases and disorders outweighs the cost of animals' lives. However, looking at the situation in another light, animals used for all types of biomedical research is less than 1% of the number of animals killed for food in the United States alone (Bear, Connors, & Paradiso, 2007). By using the ethical guidelines for animal research, animal lives are considered and animals are only used as research subjects if absolutely necessary. In scientific research, limited amounts of animal harm are accepted in exchange for a potential increase of knowledge.

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The ethical concerns centered on human and animal research are fairly common and have been given far greater attention in other works. I have chosen not to delve into the ethical concerns of scientific research because of more pointed ethical questions regarding the overarching goal of this thesis, to find a treatment for PTSD.

Before I move into other ethical questions associated with attempts to find a treatment for PTSD, it is important to note that all ethical guidelines for animal

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research were upheld in the study I completed. My study was looking to gain a better understanding of the neurochemistry of PTSD and to test propranolol as an experimental treatment for PTSD symptoms in rats. Both of these goals were accomplished, and the research that I completed would not meet the ethical guidelines to test humans. Also in accordance with the responsibilities held by the researcher, I did my best to minimize any pain or distress the animals may experience. The animals were appropriately nourished and housed, and I did not subject any animals to any threatening experiences outside of the experimental procedure. Before beginning my experiment, I explored all possible alternatives to the use of animals in my study. Given the nature of the topic and the focus of my study, I was led to use animals in my study, but did not violate any of the aforementioned ethical criteria for conducting research using animals as research subjects.

My study and overall thesis topic sparks questions surrounding the ethics of treating PTSD as well as those concerning animal research. On first glance, it appears justifiable for an individual suffering from PTSD to want his or her premorbid quality of life, meaning the symptoms from PTSD should be treated. If a person had a broken leg, he or she would have that leg casted, set back in

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place, and ultimately corrected. The decision to treat mental injuries, especially PTSD, is not quite that simple. The main side effect of prospective pharmacological PTSD treatments is either memory loss or the loss of the emotional connection to the traumatic memory (Cukor, Spitalnick, Difede, Rizzo, & Rothbaum, 2009). The value of one's memories and emotions are terribly important however. A person is only who he or she is because of his or her previous experiences, the memories of those experiences, and how he or she feels about those experiences. Altering or *fixing* one's mental illness by means of memory erasure is quite different than fixing a physical injury because mental abilities create the personal identity of the person affected by the injury. Due to the value of one's memories and emotions, the search for a PTSD treatment may be complicated by whether or not a person is willing to forget one of his or her life's most influential experiences. In other words, if one's memory of, or the emotional connection to, the experience must go, is it still best for the PTSD victim to be pharmacologically treated? Conversely, is there a value in enduring and working through suffering, via therapy options, to alter one's attitude about the trauma and overcome one's symptoms without taking a drug?

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If it is decided that it is best to pharmacologically treat the patient, another question is raised. Who do you treat and when? In addition to memory loss, many of these drugs and treatment strategies must be administered either before or immediately following the trauma. If a drug must be administered before or immediately following the trauma, how does one choose who does and does not receive the treatment? What scenarios would qualify a person for this type of preventative treatment? If a drug were to be administered post-trauma, a person would need to be able to give informed consent, which could present another issue with administration. After a traumatic experience, a person may not be in the state of mind necessary to give informed consent to the physicians. Although it seems simple at first glance, there are many questions that must be answered and ethical concerns that must be explored before a treatment for PTSD may be brought to the public.

The first question to concentrate on is the cost of a treatment for PTSD and the potential value of suffering. In the study that I completed, I did not see an effect of propranolol on all PTSD symptoms. Although this research did not support the hypothesis I set out to address, I am not entirely certain that this failure to find a consistent working treatment for PTSD disadvantages PTSD

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victims or society. Although it may be crystal clear to many people that PTSD victims need a drug rather than a therapy, I am not certain that is the case. Before I proceed further with this line of thought, I must say that I do not have a personal connection to anyone with PTSD, and I am not attempting to speak as if I do have such a connection. Clearly, the types of traumas that dispose an individual to the suffering characterized by PTSD are horrific. I also can attempt to understand the difficulties that a PTSD victim suffers on a daily basis. Yet, I am uncertain that a pharmacological treatment for the disorder is the correct answer to the problem.

The most promising treatments for the 5.2 million Americans suffering from PTSD are memory attenuating drugs. These drugs, one of which is propranolol, have shown limited evidence that PTSD symptoms can be reduced due to the numbing of emotions involved with the memory (Henry, Fishman, & Youngner, 2007). However there is also some concern that such drugs may lead to complete memory loss for a period of time (President's Council on Bioethics, 2003). As a result, the value of emotions and memories has been brought into the discussion of PTSD treatment. If an individual loses his or her emotional connections to a memory or loses the memory completely, there may be legal

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implications. In addition to these topics, it is important to consider the lessons an individual learns as a result of a trauma and how these lessons further complicate whether or not one's memories should be altered in an attempt to treat PTSD symptoms.

It is important to consider the moral costs that may accompany a pharmacological treatment for PTSD. A PTSD-eliminating drug has many repercussions for the victim concerning life after the trauma. The opposition for pharmacologically treating PTSD leads me to question how an effort to help a PTSD victim may transform into harming the individual and, in turn, society by the removal of that individual's connection to the experience. If every victim of a trauma were to alter his or her memory of the event, the overall impression of the trauma would be altered as well. In order to answer this question, I believe one must explore the value of suffering while remaining conscious to the fact that 5.2 million Americans are currently suffering from an event that has already come and gone, but still remaining present in their uncontrollable memory.

## II. What is the value of suffering?

Before attempting to find value in suffering, it is necessary to establish an understanding of what I mean by *suffering*. Although a person may be said to *suffer* a broken arm or a sprained ankle, physical pain is not typically what someone is referring to when he or she says that there is suffering all over the world. There is a difference between being hurt and suffering. A physical pain may hurt, but for suffering to result from an experience a psychological pain must exist as well. Physical hurt and suffering are connected, but separate phenomena. As I use the term, *suffering* does not reference physical pain in itself, but psychological traumas that result from biological malfunctions within the brain. Suffering is a recently orphaned child whose parents were slaughtered during a robbery. It is the pain of the people affected by genocide and a wounded veteran trying to forget the travesties of war. Suffering also ensues after the loss of a loved one or the permanent loss of one's physical capabilities. Although one may physically see the sorrow and distress brought on by the suffering, suffering itself resides within the mind. Suffering results from feelings of depletion, loss of meaningfulness, and lack of identity. Although these examples may detail a physical pain, they also deal with a certain type of

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psychological hardship. The newly orphaned child is forced to deal with feelings of loneliness, helplessness, and abandonment. Likewise, a population affected by genocide must deal with thoughts of powerlessness and the war veteran must overcome the evils witnessed in war. Losing a loved one or a person's ability to function completely alters the life of the individual, and he or she is forced to recreate his or her identity and meaning in life. In generalized, more abstract terms, suffering is the form that a memory takes when it is charged with negative emotion.

All people suffer to some degree, but the type of suffering that is endured by PTSD victims is the result of biological malfunctions that cause a single moment in time to be relived unconsciously and uncontrollably. A desire of the body is to maintain equilibrium. The body attempts to avoid the emotional charging of negative emotions and minimize suffering. The human mind attempts to maintain equilibrium between memory and oblivion and rejects irrelevant or disruptive memories (Evers, 2007). The extensive amounts of stress hormones released at the time of a traumatic event lead to an inability to reject the memory, and subsequently give rise to a powerful memory which continually replays in the individual's head (Heim & Nemeroff, 2009). At this point, PTSD develops and suffering ensues. PTSD is a severe form of suffering,

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and due to this severity, the initial response is that the suffering must be treated in a way that returns the victim to his or her pre-morbid style of living. After all, since PTSD is detrimental and results from biological malfunctions, a drug should be developed to correct those malfunctions, right?

The degree of dysfunction that suffering can cause for those suffering from its most severe forms makes it important to attempt to find value in suffering. Suffering causes a great deal of psychological pain and in many cases, physical pain as well. For instance, consider an example of human suffering that Fyodor Dostoyevsky outlines through the words of Ivan in Book V of *The Brothers Karamazov*:

*Imagine a trembling mother with her baby in her arms, a circle of invading Turks around her... pet the baby, laugh to make it laugh. They succeed; the baby laughs. At that moment, a Turk points a pistol four inches from the baby's face. The baby laughs with glee, holds out its little hands to the pistol, and he pulls the trigger in the baby's face and blows out its brains (1880).*

The imagery of this scene evokes sorrow for the naïve child, but attempt to imagine the heart-break that the mother must feel and the subsequent suffering that will surely ensue. Furthermore, attempt to imagine living with that memory constantly replaying in your mind for the rest of your life. These situations support the desire to eliminate suffering. A single case of PTSD and the

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experiences leading up to this psychological trauma cause any observer to ask: *who deserves this?* No person deserves to suffer in this manner, but suffering remains a part of daily life due to the free will of humankind. With free will, evil is a part of the human condition, and due to this evil suffering enters into the world. Since evil continues to exist, the goal is to overcome suffering and to find value in life in the midst of suffering. Alone there is no value in suffering. No person can honestly claim that there is value in a mother watching her child be executed in front of her eyes. However, there is value in the process of overcoming suffering by addressing the traumatic experience and attempting to move forward to find meaning as a result of that experience.

While free will allows suffering to enter into the world, it also allows for pleasure, love, and positivity. In *Man's Search for Meaning*, Dr. Viktor Frankl exhibits how free will can lead to drastically different outcomes. Frankl states, "Man is that being who invented the gas chambers of Aushwitz; however, he is also that being who entered those gas chambers upright, with the Lord's Prayer or the Shema Yisrael on his lips" (1985, p.157). Free will allows for suffering, but it also provides an individual the option of offering love to a fallen war veteran or a woman who was not given a choice. Free will allows an individual to show love to those who are suffering and to have a voice in advocating a treatment for

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disorders such as PTSD. Through free will a person has the choice to react to each experience as he or she wishes. With the freedom of choice comes the freedom of opportunity, both good and bad. Freedom may lead to suffering, but it also provides the opportunity to rush toward meaning.

Through free will, a person is provided the opportunity to react to each scenario in the way that he or she chooses. There are two methods by which a victim may choose to move past the reliving of traumatic memories. One way is to mitigate suffering with a pharmacological treatment, such as propranolol. Through such a treatment, a person may never develop the traumatic memories that perpetuate suffering. Another option is to work through one's suffering rather than taking a drug, and realizing that the trauma is now in the past, that each day is a brand new day, and that there is meaning in the life that still lies ahead. In other words, one may work to overcome his or her suffering to find meaning.

Overcoming suffering without a treatment is tough but not impossible. What does it mean to overcome suffering? Overcoming suffering means recognizing that a trauma occurred, understanding that there is suffering attached to that trauma, and realizing that one can reduce his or her suffering by

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changing his or her relationship with the traumatic experience. While this is easier said than done, it can be realized. No trauma victim is in this process alone, and needs to utilize his or her support system to help get him or her through this tough time. In addition to family support, individuals may look for therapeutic help.

The three most common therapy treatment methods for PTSD are cognitive behavior therapy, eye movement desensitization and reprocessing (EMDR), and stress management (Ponniah & Hollon, 2009). Trauma-focused cognitive behavior therapy involves repeated exposure to the traumatic memory through cognitive methods and then progressively changing the individual's thought processes and behaviors towards the trauma. EMDR utilizes dual attention tasks to help the patient process the traumatic event. EMDR involves the patient focusing on negative trauma-related memories while engaging in a task involving some form of bilateral stimulation, such as eye movements, until distress has decreased and belief in more positive trauma-related thoughts has increased. Stress management does not focus on the trauma, but involves the patient's learning skills to help manage anxiety. Such skills consist of slow, abdominal breathing, relaxation techniques, learning to use positive statements and self-talk strategies, distraction techniques, and assertiveness training.

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Therapies such as these help trauma victims manage and eventually overcome their suffering. Once suffering is overcome, meaning may be found in the individual's renewed appreciation for life absent of suffering.

Despite the intentions of these therapeutic treatments, the efficacy of these therapies is not ideal. Although these therapies prove helpful for some patients suffering from PTSD, 30% of patients who develop PTSD will still be suffering from treatment ten years following the trauma (Langevin, De Salles, Kosoyan, & Krahl, 2010, p. 1241). These individuals may not have received therapy or followed through with their therapy, but regardless, 30% is a large number of PTSD victims with chronic symptoms. For this reason, current research surrounding prevention strategies for PTSD has concentrated its efforts on pharmacological treatments.

The goal of a preventative pharmacological treatment is to alter one's memories, effectively inhibiting PTSD symptoms. Researchers and physicians are looking at experimental drugs that may numb the emotions associated with a patient's memories or perhaps eliminate recollection of the traumatic memory entirely. It is not practical to erase a patient's past memories. However,

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eliminating a group of memories that relate to a tormenting period of a patient's life is not out of the question.

Research has progressed in identifying potential drugs that may be utilized as preventative PTSD treatments. Over the past decade, corticosteroids, beta-adrenergic antagonists (propranolol), and opiate analgesics (morphine) have been shown to reduce hormonally enhanced memories and fear conditioning (Cohen et al., 2010). Other drugs such as D-cycloserine, a NMDA receptor agonist, Ketamine, an NMDA receptor antagonist, Praosin, an alpha-1 adrenergic receptor antagonist, and Ecstasy have all shown promise in selectively altering individual's memories and reducing PTSD symptom severity.

The discovery of a drug that would allow people who experience a traumatic event to continue on with their lives rather than develop PTSD would be a great finding. With such a treatment, there may be a way for the mother, who saw her baby executed at point blank, to have peace of mind. Although this does not completely eliminate traumatic events, it does eliminate the day to day struggles that a person may face as a result of such events. If the mother does not remember seeing her baby taken from her, she is much less likely to suffer. In much the same way, a war veteran with PTSD may finally be able to sleep through the night without revisiting Vietnam. To rid an individual of his or her

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suffering is to give the individual a renewed quality of life. Clearly, such a treatment has great potential for improving the lives of many.

The benefits of eliminating suffering are evident, but there are also arguments warning against such action. Whether one's memories are excruciating, glorious, or both, experience is what shapes who an individual becomes and how that individual derives meaning from life. Suffering is only known as a result of the knowledge and memories of the way things were before a certain traumatic event. Each individual is who he or she is, at this moment, because of his or her memories of the experiences that he or she has encountered.

Memory has a tremendous value regarding who we are as human beings. In *The Use and Abuse of History*, Nietzsche speaks of history, or memory, and proceeds to pose a question. Nietzsche asks if you would rather live as a cow simply living in the moment feeding on hay or as you are with all your thoughts, worries, and concerns. According to Nietzsche, man envies the "beast's happiness," but would never change places with the beast (1874). Nietzsche suggests that memories are worth the cost of unhappiness because there is value in knowledge of the past, and this knowledge adds depth to each person.

A major criticism of a possible PTSD treatment is that it may eliminate a crucial memory to the individual's life. Nietzsche is also quick to point out that

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forgetting helps make a person who he or she is along with memories. Some things in life must not be remembered. The true question is which memories should be remembered and which ones forgotten. It may be argued that if a memory is going to be forgotten, why not a painful memory? Yet it may be argued just as strongly that a traumatic memory affects an individual the way it does for a greater reason. Should an individual eliminate a memory that will have a truly profound impact on his or her life, even if there may be potential suffering as a result of that memory? For the majority of PTSD victims, I believe that the experience should be worked through because meaning can be derived from the experience. However, if a person believes that he or she cannot live with his or her suffering, it may be best for that person to eliminate the traumatic memory. There is no value in suffering alone. The value associated with suffering is found through the transformation of one's outlook on life and the discovery of meaning.

The other mechanism through which a PTSD treatment may work is by numbing the emotional impacts of a memory. Opposition to this approach surrounds the idea that one's emotions are intimately linked to his or her outlook on the world. Hurley (2007) explains that emotions are often seen as an individual's understanding of his or her circumstances. For instance, a person

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may be afraid because there is an immediate threat. Additionally, emotions serve evaluative purposes. Emotions show the values that a person holds, but they are also able to change based on the circumstances of the situation. For example, a mother may show compassion to her son struggling with PTSD after returning home from war. Emotions serve vital purposes in human lives.

The elimination of one memory's emotional associations would not contribute to personal change in the same way as the erasing of an entire memory would, but it would change the relationship to a traumatic event. For example, if a rape victim was treated with propranolol immediately following being raped, and did not have any emotional connection to the incident, she might not be able to realize fully the horror of the event that happened to her. She may know that rape is a terrible act because she has been told so, but she may not know this personally due to her lack of a negative emotional experience to being raped. If she was raped and did not have an adverse reaction to the event, the general opinion that rape is bad may be challenged by the individual's lack of emotions related to the experience. The loss of one emotional connection may not greatly influence society, but the cumulative loss of all the emotional connections of all the traumatic experiences of all victims with PTSD would have a profound effect on society. Using the same example, if no rape victim had a

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negative emotional connection to the event because each rape victim was given a memory altering drug to repress the effects of the sexual event, rape may not be viewed as such an evil act. Emotions play a major role in humans' lives and are as crucial as memories to an individual's identity.

The answer to overcoming suffering does not lie in eliminating the memory of the trauma or preventing a memory from developing, but in deriving meaning from the events that have occurred and altering one's relationship with the traumatic event. Suffering is the form that a memory takes when it is extremely charged with negative emotion. One's memories play a huge role in suffering. It is impossible to eliminate or even lessen suffering unless one is willing to alter the relationship one has to his or her memories. It is one's memory that provides a reference for what does and does not cause suffering. Memories of good and bad times, and feelings of disappointment, anger, suffering, or any other emotion are only understood because of previous experiences. In addition to providing a reference point, memory provides the narrative that continually influences suffering. As long as one maintains a negative relationship with the event that caused his or her suffering, the suffering has potential to exist in a harmful way. However, the negative

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relationship does not have to exist forever. It is possible for a person to alter his or her attitude about a traumatic experience.

When an individual is able to live through the suffering of remembering a trauma and alter his or her attitude about a traumatic experience, posttraumatic growth occurs. Positive posttraumatic growth often co-occurs with PTSD (Levy & Clark, 2008). Although many people disregard the possibility of posttraumatic growth, the idea that tragedy can trigger personal transformation is an ancient thought occurring throughout the course of major religions, Greek tragedy, and other literatures (Tedeschi & McNally, 2011). Typically there are five domains in which trauma may elicit personal growth: renewed appreciation for life, new possibilities, enhanced personal strength, improved relationships with others, and spiritual change (Tedeschi & McNally, 2011). An example of posttraumatic growth is found in a study performed by Sledge, Boydstun, & Rabe (1980). This study interviewed aviators that were shot down, imprisoned, and tortured for years by the North Vietnamese, and of those interviewed, 61.1% reported that they had benefited psychologically from the experience. Among the reports, the aviators said that imprisonment had produced positive changes in their personalities, increased their self-confidence, and taught them what was truly important in life (Tedeschi & McNally, 2011). It is true that certain variables

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mediate posttraumatic growth, but it is a real possibility for anyone suffering from a traumatic experience. Furthermore, it is even more promising for PTSD victims that symptom severity is positively correlated with the degree of posttraumatic growth. A preventative, pharmacological treatment for PTSD would eliminate any chance for posttraumatic growth or personal change because the traumatic event would not have a great impact on the victim's life. Posttraumatic growth is another life altering effect of the trauma that would be prevented from developing along with the memory of the experience or the emotions involved. Perhaps PTSD is not a biological malfunction but a purposeful occurrence. Through dealing with one's trauma and suffering in an open, honest manner, an individual can experience posttraumatic growth and find meaning in his or her life after the trauma.

Although it is true that humans are subject to biological, psychological, and sociological conditions, certain feats are unexplainable. It is possible for an individual to live through unimaginable suffering, even if completely undeserved. In Frankl's *Man's Search for Meaning*, Nietzsche is quoted as saying, "He who has a *why* to live for can bear with almost any *how*" (Frankl, 1985). It may be unexplainable, but any individual can live through any amount of

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psychological suffering as long as he or she has the will to do so, which is illustrated through research on posttraumatic growth.

In respect to the values of memories and emotions as well as the possibility of posttraumatic growth, it may be that the argument for the elimination of suffering is not as simple as originally thought. The question quickly evolves from a purely scientific one regarding the definition and treatment of suffering to a question fully invested in the essence of whom the patient is and his or her meaning in life. Before a person can begin to contemplate a treatment for suffering, he or she must decide what he or she believes his or her experiences are worth. Is it best to eliminate one's pain or fully invest in the experience and work to overcome the suffering that accompanies the traumatic memory?

It is entirely possible to derive value from suffering, and suffering does not have to be eliminated in order to find meaning post trauma. It is important for an individual to *live* through his or her suffering because each individual has a say in what he or she will become and the changes that he or she can influence. After all, "A human being is not one thing among others; things determine each other, but man is ultimately self-determining. What he becomes—within the limits of endowment and environment—he has made out of himself" (Frankl,

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1985). Regardless of what today holds, tomorrow is a new day with new opportunities. A man has the choice to behave like a "swine" or a "saint." The individual can either choose to sit by thinking about the past or live in the present and push beyond the suffering to find meaning. The search for meaning may be accomplished by avoiding suffering through a pharmacological treatment. However, by intentionally focusing on experience and intentionally working through the hardships, the search for meaning becomes so much more informed. This choice is the individual's to make. In the case of PTSD, the victim may choose to numb his or her memories by accepting treatment or he or she may deny pharmacological treatment and seek to find meaning in life after the trauma.

The ability to use one's suffering to find meaning is predicated on one's attitude. If it is not possible for a person to find a reason to overcome his or her suffering, it is nearly impossible for him or her to see any meaning that will result from such suffering (Frankl, 1985). In this case, the PTSD victim most definitely should accept treatment and proceed on with his or her life because there is no value in suffering by itself. However, if the victim believes that he or she may find meaning in life after the trauma, then a treatment may not be necessary. Frankl explains, "The way in which a man accepts his fate and all the

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suffering it entails, the way in which he takes up his cross, gives him ample opportunity—even under the most difficult circumstances—to add a deeper meaning to his life” (1985). Frankl suggests that suffering provides an individual the unique opportunity to find meaning in life, and through the discovery of one’s meaning he or she is able to alter his or her relationship with the traumatic memory. Life is not special in itself, but living for a meaning and having the ability to live for a purpose is special. Although it is difficult to see initially, suffering may influence a new meaning in life and a new purpose of living.

Through the discovery of meaning, a victim is able to alter his or her relationship with a traumatic memory and use his or her suffering as fuel for the good that may lie ahead. It is quite difficult to see how a mother’s viewing of her child’s death can be turned into human achievement or how a war veteran may be able to transform his actions of killing in Vietnam into personal growth, but these instances do exist. Frankl makes this clear when he says, “even the helpless victim of a hopeless situation, facing a fate he cannot change, may rise above himself, may grow beyond himself, and by so doing change himself. He may turn a personal tragedy into a triumph” (1985). No matter the scenario, an individual has the opportunity to alter his or her attitude about the situation. For example, due to her child’s death, the mother previously mentioned may wish to

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adopt an orphaned child. In doing so, the mother would provide the orphan with a home and a nurturing upbringing so that he or she is aware of the justices and the injustices of the world. Likewise, the war veteran may be able to speak as an advocate to young men and women on the value of a life and in doing so, save the lives of others. It is truly difficult to overcome suffering, but if one can look at the future ahead rather than the events of the past, he or she may find meaning in life and alter this or her relationship with the traumatic memory.

Any event has the power to be transformative, and every experience contributes to who you are as a human being. The events that cause PTSD or other degrees of suffering are extremely powerful due to the emotional nature of the event. Perhaps this leads an individual to think that these events must be eliminated from one's memory. Still one may choose to use these events as powerful tools to make a personal change and create meaning. The greatest amounts of suffering have the potential to lead to the greatest degrees of posttraumatic growth, but this is only possible if one is willing to look past his or her suffering, alter his or her relationship with the traumatic event, and ultimately find meaning. If one is able to maintain the attitude necessary to find meaning, then there is most definitely value to the process of working through and overcoming the suffering that results from a traumatic event.

Through hard work and a commitment to life, I believe that any individual has the ability to overcome suffering and find meaning in life. Research shows that approximately 60% of people suffering from PTSD show evidence of posttraumatic growth, and that the degree of posttraumatic growth is positively correlated with the severity of PTSD symptoms (Tedeschi & McNally, 2011). This finding illustrates that it is possible to find a meaning in life and a reason for living, in the midst of the suffering that may ensue. The previous section's analyses support that there is value in suffering alone but that there is tremendous value in overcoming suffering by way of dealing with one's current state and working to improve one's self on a daily basis. For those who are committed to dealing with their suffering in a real, honest, and upfront manner, there is an opportunity to grow from any experience and find meaning.

Although I believe everyone can find meaning beyond trauma and suffering, I also realize that some individuals need more help than others in finding meaning. If it is true that every person has the ability to grow from any experience, why do only 60% of PTSD victims show evidence of posttraumatic

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growth? What about the other 40%? I believe that some individuals need help in their search for meaning. Some individuals suffer to such an extent that they cannot complete effortless, daily tasks or muster enough courage to simply go to bed at night. How are these individuals supposed to find meaning in such a broken life? These are the types of patients that need help to carry on; these individuals need a treatment to get them back into living life. Although current drugs threaten the victim's memories and emotions, for these particular individuals the costs associated with the drug may be outweighed by the chance of the victim returning to a version of their premorbid functioning.

Subsequently, a return to daily functioning may allow the individual to partake in activities that lead to the discovery of meaning in one's life that was inhibited by PTSD. In certain circumstances, I believe that a treatment for PTSD is needed in order for the victim to have the ability to move past his or her suffering and redeem his or her memory of the trauma.

The possibility of treating PTSD, as well as other mental disorders, ultimately relies on the victim's situation and decision of whether or not he or she can live an agreeable life without a treatment. If a person truly believes that he or she will not be able to function, and he or she is willing to lose the

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memories or emotional connections to the trauma involved, I do not believe that a person should be denied a treatment if one is available. Treatment for PTSD should be considered on a case by case basis due to the high stakes for those wishing to pursue a treatment strategy. Patients should be made aware of the possibilities of recovery without a treatment. It remains true that growth can be obtained for most PTSD cases without a pharmaceutical treatment. Yet, certain cases of PTSD are so inhibiting that they disallow the patient to live his or her life. Regardless of these patients' knowledge of potential side effects and the wider implications of these effects on society as a whole, if a treatment for PTSD is made available for those victims who cannot even sleep at night because their traumatic experience haunts their dreams, it can be expected that these individuals will choose the treatment option despite the individual and societal costs.

While uncertain that this scenario will occur due to ethical considerations, if there is enough pressure and a growing market for a PTSD, or suffering, drug to be developed, I believe that it is likely that a PTSD drug may become available. In preparation for this possible scenario, it is important for people to give serious consideration to how such a treatment could be implemented.

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Although this drug may be intended for those victims with incredibly severe versions of PTSD, it is likely that treatment will become universally available for all persons affected by PTSD.

Whether the treatment for PTSD were to become universal or simply remain available to those suffering from the most severe cases of PTSD, there are issues regarding how such a treatment could be implemented. For instance, for such a treatment to be implemented the patient would need to be able to give informed consent. This would be quite difficult seeing that the majority of experimental treatments for PTSD would need to be used within a certain time frame following the trauma. Because most individuals who go on to develop PTSD do not have the mental aptitude to give informed consent, the possibility of treatment is complicated even further. There are many concerns surrounding potential implementation strategies for preventative as well as reactive treatments for PTSD.

While I believe that a PTSD drug is far from market, I realize that certain people need a treatment in order to move on with their lives. Once need becomes too large for society to ignore, a treatment for PTSD is likely to be given more attention. Before this occurs, it is important to be proactive and call attention to

the possible complications concerning the implementation of a PTSD medication. In the following section, I will provide an overview of the possible issues about PTSD treatment implementation as well as a hypothesis of how a PTSD treatment may be implemented justly.

### **III. How could a treatment for PTSD be implemented ethically and justly?**

It may be true that science is far from curing PTSD, but it may also be true that society is close to seeing a treatment for PTSD on the market. It is yet to be seen when or if a treatment for PTSD will be developed and implemented. However, it is never too early to think how a drug may be implemented and how the implementation of that drug may affect society. If one believes that he or she cannot function without medication or that the reclaiming of their previous life is greater than the cost of losing one's memory, a PTSD treatment may be developed to diminish or eliminate PTSD symptoms when the drug is given immediately after the trauma. Such a drug could potentially alleviate suffering for millions of individuals. This sort of treatment has ethical concerns due in part to the potential inability to give informed consent. A solution to this ethical dilemma may be to provide a preventative rather than reactive drug for PTSD. If

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you could give each individual about to enter a potentially traumatic environment or situation a drug which would prevent any chance of the development of PTSD, PTSD would cease to be an issue. However, this implementation strategy also has widespread ethical concerns. For instance, how does one decide which individuals receive the treatment? What constitutes a *traumatic environment or situation*? How would a preventative treatment for PTSD affect society? These are important questions to consider and the aim of this section. I believe that there are individuals in absolute need of a treatment for PTSD. However, I do not think there is a foolproof process of implementation for such a treatment.

Theoretically, the prevention of PTSD may be accomplished either by providing a treatment prior to the trauma or by providing a treatment in response to a traumatic event. Henry et al. (2007) reports that the strength of a memory is directly correlated with the release of endogenous hormones such as adrenaline. During a stressful situation, an over-release of adrenaline occurs and this results in elevated levels of noradrenaline. This elevated level is what is thought to perpetuate the over consolidation of the memory and cause PTSD (Henry et al., 2007). If a treatment, such as a beta-adrenergic antagonist, is used

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to prevent this process of over-consolidation from occurring, the enhanced memory as well as the PTSD symptoms may be eliminated. Thus, it is thought that a preemptive attempt to treat PTSD would be the most effective. Following this line of thought, several studies have successfully prevented the development of PTSD by administering a preventative treatment before subjecting the subject to the experimental trauma (Cahill et al., 2002; Maheu et al., 2005; Reist et al., 2001; van Stegeren et al., 2005).

Strictly looking at the neurological mechanisms through which it is believed that PTSD results, it seems that treatments for PTSD should be preventative in nature. Yet, in a social context, this conclusion is not so easily reached. If a treatment is given prior to a traumatic experience, it must be known that there is a good chance that a traumatic event will occur. In the case of many traumatic events, such as natural disasters and car accidents, this knowledge is unavailable. Yet in certain circumstances, it may be concluded that a traumatic event is likely to occur. Individuals in the fire, law enforcement, military, and rescue fields may benefit from a preventative treatment of PTSD because these professions typically increase the probability of being exposed to a traumatic event. Individuals such as these may be treated with short-term memory

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suppressors prior to entering a situation that could potentially put them at risk for developing PTSD. This initially sounds like a fantastic option, but one must remember that any current PTSD treatment either blunts the victims' memories or the emotions involved with those memories. These remain to be huge side effects not to be taken lightly. Additionally, both short and long term side effects of repeated usage of such a drug remain unknown.

Although a preventative treatment for PTSD may be most effective, it may not be the most advantageous treatment strategy. If one attempts to reduce suffering through preemptive intervention, many questions arise. First, how do you decide who receives a preventive PTSD treatment? What are the criteria for being eligible for such a treatment? Perhaps you only administer such a treatment to individuals whose jobs entail regular exposure to traumatic experiences. If this is the case, how do you decide what regular exposure to traumatic experiences means? Because of the importance of memories to an individual and society, a line must be drawn so that the elimination of memory, whether traumatic or not, is not as accessible as the elimination of a headache.

In addition to the unsolved questions regarding implementation, the preventive strategy to treating PTSD may have wide ranging impacts on society.

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If large groups of people are treated for PTSD, they will not suffer as much. They also may not remember the events that occurred or their emotional feelings about those events. Since the people who may be treated pre trauma are the individuals in rescue, protection, and law enforcement roles, these side effects may create huge consequences for society. For example, in the court of law, these individuals often have to give testimony, but this could not be justly achieved if their memory of the situation had been impaired in any way. This problem would become much larger if this form of PTSD treatment was made available to a wider group of people. A preemptive treatment strategy for PTSD does not only have implementation issues but may negatively impact society as well.

The other viable option for treating PTSD, as previously mentioned, is to do so after the traumatic event has occurred. This treatment also aims to reduce the amount of noradrenaline produced in response to stress. Although providing treatment post stress is less effective in reducing the consolidation of memory, it still has memory blunting effects and may be an effective strategy for treating PTSD. Treating PTSD victims post trauma removes much of the issue of determining who should and should not be treated. For instance, with this treatment strategy, not every firefighter, police officer, or soldier would be given

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a memory repressing drug. Instead, only those that have been exposed to an excruciating trauma or wish to receive the treatment after the trauma would be given the drug. This strategy would reduce the amount of emotionally blunted memories. Thus, the impact on society would not be as great, and the implications of PTSD treatment outside that of the victim's life are not controversial.

A post trauma PTSD prevention strategy must be advantageous for the individual in order to be implemented. At the conclusion of section III, I concluded that the majority of PTSD victims grow from the traumatic experience causing their PTSD symptoms but that some individuals do not show any posttraumatic growth and require a PTSD treatment in order to determine meaning from their traumatic experience. It is not possible to reduce the consolidation of memory years after the trauma has occurred. In order to reduce PTSD symptoms, the treatment must be administered either prior to or immediately following the traumatic experience. Thus, a reactive treatment to a traumatic event does not allow the individual the opportunity to respond to the event either positively or negatively. Unlike a preventative treatment, the post trauma treatment strategy does still allow the victim or those connected to the

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victim to determine how severe the traumatic experience has been and if the victim should be given a memory repressing treatment. Although there is no sure fire method of determining if a person will develop PTSD in isolation or in combination with posttraumatic growth, with the reactive treatment strategy, each victim has the ability to choose whether or not to receive treatment.

A reactive PTSD treatment strategy thus limits the impacts of a PTSD treatment on society while allowing for an individual to choose whether to endure the suffering and traumatic memory or to administer a PTSD symptom reducing treatment. This is not to say that this strategy is without concern. Like the preemptive PTSD treatment strategy, the reactive PTSD treatment strategy has an issue with implementation, informed consent. Following a traumatic experience, especially one that results in the most severe forms of PTSD, the victim is not likely to be in any emotional state to give informed consent. This inability of a victim to give informed consent is a major hesitation in the treatment of PTSD.

Informed consent is the medical avenue through which a treatment may be made available to a patient. However, informed consent requires the patient to decide what his or her best option is. Does the patient wish to be treated or

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not? Supady, Voelkel, Witzel, Gubka, and Northoff (2011) state that decision making is the crucial psychological process in informed consent. The United States, as well as other Western countries, adheres to a mandatory model of autonomy. This means that patients have the right to make informed choices for themselves. The traditional, paternalistic model of medical decision making differs from the autonomous model by mandating doctors to choose which option is most advantageous for the patient. According to this view, patients are cognitively and emotionally unprepared to make decisions in their best interest (Botti, Orfali, & Iyengar, 2009). Although United State's doctors still take the Hippocratic Oath to "follow that system of regimen which, according to my ability and judgment, I consider for the benefit of my patients," it has been decided that patient's values should also be given greater value than the knowledge of the medical staff (Oath of Hippocrates, ca. 400 BC/1910). This is in large part due to the Kantian philosophy that people are not merely a means, but an end in themselves. A doctor may aid in the decision process, but ultimately, the decision is not the doctor's to make. Thus, the mandatory model of autonomy presupposes that patients know their risk aversion and desired quality of life better than doctors. Individuals must make educated, informed decisions. This may be accomplished with the help of doctors' advice, but a patient must also

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reflect on his or her own values and decide whether or not to take a treatment. If the patient is not in a position to make this decision, it is up to the patient's family or the doctor to make this tough decision.

Although the paternalistic model of medical decision making has technically departed from medical practice in the United States, glimmers of it still exist. Doctors still have a great impact on their patients' decisions. There are a few doctors who choose to give patients, and their families, the best available data, untainted by the doctor's perspective, in order to let the family and patient determine the best option as it fits with their value system. Most doctors, realize that complex decisions are emotionally taxing, and the patient may not be prepared to fully make the decision. Ubel and Loewenstein (1997) recap an area of cognitive psychology research that has shown that people are rapidly overwhelmed by having to consider more than a few options, and quickly resort to simplifying strategies that ignore pieces of the information. For this reason, many doctors choose to provide their professional perspective on the possible options at hand. Hopefully, through this unbiased medical advice, the family can make an educated decision in determining if the patient should or should not receive the treatment.

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It is important for the doctor to remain emotionally detached from the patient's available options, but it is also important for the doctor to provide information concerning all possible future outcomes in addition to his or her medical advice to the patient and the patient's family. I believe that a PTSD victim can only make an informed decision on whether or not to receive treatment if he or she is able to understand all of the options for his or her future. This is a difficult concept to grasp, but I believe that the decision to be treated for the possible development of PTSD is also difficult. It should not be an easy decision to completely eliminate the emotional connections it has on a memory or to eliminate the opportunity of growing out of an experience. All in all, informed consent should be taken very seriously especially for those individuals that are at risk for developing PTSD. I believe that the traumatized individual is the only person that has the ability to fully make the decision to administer a treatment but also realize that this option is not available for the greatest types of traumas.

In the cases where the traumatized individual is unconscious or emotionally unavailable to give informed consent, I believe that it is up to the family and friends to make the decision for the victim. In my opinion, the doctor

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should not be making such a decision. The expression of PTSD is not a life threatening illness but a lifestyle altering disorder. It is terrible that some individuals perpetually suffer from a traumatic experience, but it is also miraculous for individuals to overcome their suffering and experience posttraumatic growth through the discovery of meaning. When a doctor is faced with the decision of providing a memory repressing drug and altering a patient's remembrance of a major event in his or her life, I hope that the doctor will let life take its course rather than imparting his or her own beliefs on the situation.

The process of treating PTSD is a complicated one. It is not beneficial for society to universally provide a memory-repressing drug for all people that may develop PTSD. In fact, I believe that a treatment for PTSD symptoms only has the potential to be beneficial as long as it leads the individual to personal growth. I personally believe that the premature treatment of PTSD symptoms, whether prior to or following a trauma, is not the route to develop. I believe that the search for meaning and the process of aiding people in dealing with their suffering and traumatic memories are the area in which research should be focused. Helping the suffering by way of a pharmacological treatment is an admirable goal, but the discovery of a pharmacological treatment to reduce

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PTSD symptoms is not the only way to provide help. The methods in which we can help those suffering from PTSD are numerous. A pharmacological treatment may be the answer some day, but today there are too many issues and ethical concerns to develop a treatment. Some of the questions and concerns regarding preventative treatments may be resolved, but I do not believe that society is at a place to implement such a treatment. It is important to keep focusing on asking the tough questions surrounding the treatment of disorders such as PTSD.

Without giving thought to the issues at hand, no treatment will ever surface, PTSD will continue to remain untreatable, and the 40% of PTSD victims that do not experience posttraumatic growth will continue struggling through life.

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The past three sections covered a myriad of topics including scientific research, animals as research subjects, the value of overcoming human suffering, posttraumatic growth, and the implementation of possible PTSD treatments. Additionally, I have explored the thoughts of others while sharing what my beliefs are regarding the issues. However, I do not believe I have fully integrated

the past three sections or conveyed what I believe the next steps are for the researchers, medical professionals, victims, and general public in dealing with PTSD. In the final section of this afterword, I will address these questions and begin to bring this thesis to a close.

#### IV. **What does this all mean, and what is next?**

In *For the Time Being*, Annie Dillard explains that “to save a life is to save the entire world” (2000). This statement may be seen as support for a PTSD preventing drug. After all, a pharmacological treatment for PTSD may save the quality of life that the trauma victim is used to living. However, this statement may also be seen as support for the process of overcoming suffering. Perhaps it is not up to a drug, but rather up to the individual and his or her family and friends to save a life. It may be that we are all called to help each other while we are in need, and if we each can save, or help, a single life, then we will save the world.

After conducting my own research and exploring the ethical questions surrounding pharmacological PTSD treatments, I have formed to the opinion that a preventative treatment for PTSD should not be made available universally

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because: 1) there are high costs associated with the altering of traumatic memories, 2) there would be tremendous implementation problems in administering a preventative drug, and 3) In my opinion, the process of overcoming suffering is a vital part of life. I believe that there are way too many costs and limitations associated with a preventative treatment of PTSD.

Additionally, I would rather encourage growth by bettering the therapies available than eliminating suffering with a pill. I also believe that the search for a pharmacological treatment for PTSD should not completely be abandoned. If a drug is someday developed to rid an individual of a single memory of an event from years prior, I believe that this is an avenue to treating PTSD without the tremendous costs, ethical concerns, and implementation issues.

Although there are 5.2 million people suffering from PTSD in the United States alone, and many of these individuals' symptoms will remain chronic, I believe that there is great value in working to change one's relationship to the traumatic experience. Suffering is a common misfortune of the world, no individual should be forced to endure it in any shape or form, and it is an admirable goal to attempt to rid the world of the memories that influence suffering. However, I do not believe the mechanism used to alleviate suffering should be a pill that attempts to purge the world from traumatic memories.

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Suffering serves as a main avenue for the discovery of meaning in life and the pursuit of Magis. I believe that God allows free will, and thus suffering. A person can only recognize injustice in comparison to justice. Although freedom allows us to influence suffering, it also allows us to be Gods hands; "It is up to us, what God will see and hear, up to us, what God will do. Humanity is the organ of consciousness of the universe...Without our eyes, the Holy One of being would be blind" (Dillard, 2000, p.196). While today's world, and every life in this world, is full of suffering and injustice, it can be changed without numbing the effects of evil actions or erasing one's memories. A drug is not needed to eliminate suffering.

My recommendation is to concentrate one's efforts on improving the cognitive and behavioral therapies available to treat PTSD and to concentrate pharmacological research efforts on a reactive treatment to PTSD rather than a preventative treatment. Currently, the efficacy of therapies used to treat PTSD is questionable to say the least. PTSD has a lifetime prevalence of approximately 6.8% in the United States and a 12 month prevalence of 3.8% (Adamec, Muir, Grimes, & Pearcey, 2007). This equates to 5.2 million people suffering from PTSD in the United States. Of these 5.2 million people, 30% of them will still be suffering from PTSD symptoms 10 years from now, and their symptoms are

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likely to remain chronic (Langevin, De Salles, Kosoyan, & Krahl, 2010). These statistics show that the current treatments of treating PTSD are not effective at this time and that greater research on ways to develop therapeutic treatment options as pharmacological options should be completed.

In regards to possible pharmacological treatments, I believe that the area of focus needs to be on reactive treatments for PTSD. Such a treatment would lessen PTSD symptoms, even years after the trauma has occurred. This may seem like a fairytale treatment, but this is where the research has begun to shift. Research has attempted to single in on how long-term memory is stored, and the claim has been made that PKM-zeta is a crucial protein kinase in this process (Lisman, 2012). Furthermore, research has shown that the inhibition of this kinase, with ZIP, which is a membrane permeable peptide inhibitor of PKM-zeta, leads to the reduction of memory. When ZIP is administered immediately following an event or weeks to months afterward (when remembering the event) the subsequent memory of the event is eliminated (Shema, Kacktor, & Dudai, 2007; Cohen et al., 2012). PTSD treatment research is moving in a positive direction. However, I still believe that the goal should not simply be to cure an individual's symptoms but to help the individual grow out of his or her experiences and find meaning out of his or her suffering.

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Although the research has begun to shift away from developing a preventative treatment for PTSD, it is still important to continue asking the difficult questions about potential treatments. It is important to realize that there is value in overcoming suffering. Although every individual should be able to function normally, suffering is a vital part of the human condition. Posttraumatic growth can be achieved in response to this suffering. In order for people to continue asking difficult questions, society needs a fundamental change of attitude. Frankl points out that "Life ultimately means taking the responsibility to find the right answer to its problems and fulfill the tasks which it constantly sets for each individual" (1985, p. 98). Each individual must realize his or her speck of the world and work to redeem his or her place. This may be support for an individual suffering from PTSD, a PTSD victim addressing his own struggles in a real and honest manner, or it may not have anything to do with PTSD. Regardless of circumstance, each individual has the ability to redeem a small portion of the world. Without question, the world can be a dark place, but sometimes it takes suffering to truly see the light that may be uncovered in the darkness. PTSD research must continue, but regardless of its outcome, individuals must continue working through suffering in a real and honest manner.

**Concluding Remarks:  
How a thesis helps find meaning...**

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Upon completing this thesis project, I can honestly say that no other class, project, or assignment has contributed as much to my learning and personal growth as this project. Through the course and past fourteen months, I have learned much about PTSD and the possible treatments of the disorder, realized that the philosophical exploration of questions is just as important as scientific studies, and most of all, uncovered much about myself. Through the completion of this thesis, I have gained a better understanding of what I wish to do in the future and what my search for meaning entails. Just as I began this thesis project with a hope to integrate my beliefs into my thesis work, I look to conclude this thesis with a hope to continue questioning the topics that I have explored in this thesis, to continue to grow as a person, and to move forward in the search of meaning.

My thesis project began with the scientific research I conducted on *The effects of propranolol, a non-selective  $\beta$ -adrenergic antagonist, on rat behavior in an animal model of posttraumatic stress disorder*. This study allowed me the opportunity to grow as a neuroscience student, to gain valuable research experience, and to learn about a psychological disorder that is important to me and an issue for those suffering from the disorder. Although I did not support

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the hypotheses that I set at the onset of the study, I found significance in other areas of the study. According to the data collected, propranolol does not have a significant effect on PTSD-like symptoms in rats. The data also suggests that the animal model may not have sufficiently produced a model of PTSD. However, the present study did yield data concerning the time course of the presentation of PTSD-like symptoms, and also provided data suggesting that laboratory animals may perpetually be in a state of anxiety, potentially an animal-version of PTSD. This study challenged me to take the neuroscience knowledge I have learned in the classroom and apply it to real world issues. Through the process of designing and then carrying out a study, I have gained valuable research experience that I can take with me into my next stages of life. Through this study and greater thesis project, I have learned a lot about what it takes to further knowledge through scientific research.

The study I conducted, as well as the greater thesis, revealed a lot of information about PTSD that I had not previously known. I have learned a great amount about the possible neurobiological mechanisms through which PTSD may be influenced. Additionally, I have learned that there is not and cannot be, at the current time, an adequate treatment for PTSD. Although there have been

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many advances in research regarding the topic, no treatment has proved effective for the preventative or reactive treatment of the disorder minus significant side effects. On a more elementary level, this thesis has opened my eyes to the prevalence of PTSD and the issues that it creates for those suffering from the disorder and others involved in their lives.

As I mentioned earlier, PTSD is an important topic for me. Although I do not have a relative suffering from PTSD, I do have three uncles and an aunt in the military, and my future career plans may include the military as well. I believe that I am blessed for not having to see them suffer from this disorder, but I know that they are at a greater risk for developing PTSD at some point during their lives. As I have gained a greater knowledge of the disorder, I have become aware of the issues that it may create and the struggles that are involved with overcoming one's symptoms. I also know that I am passionate about easing suffering and continuing the work I have began in this thesis. In many ways, this thesis has influenced my outlook on the future.

Although this thesis has not changed my career plans of becoming a physical therapist, it has managed to change my outlook on the way I will live my life going forward. The researcher's primary influence on my future is the

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latent idea of allowing life to happen and learning from every experience. In the study, I did not find the results that I believed I would, but I did find other data that can inform PTSD research as well as the field of neuroscience. I believe that life often times throws curve balls, and although one may be completely prepared, things can go contrary to planned. As I move forward, I will prepare for the future, but I will also learn from every instant, be flexible with the course that life takes, and be ready to take advantage of each stage of life.

The philosophical questions raised in *The Afterword* of this thesis, influence my life even more so than the research at the foundation of my thesis. Through the philosophical questions, I have learned that it is most important to ask tough questions and to formulate one's own answers to those questions. From the scientific standpoint, it seems great to eliminate suffering and it is fascinating that a drug can numb the emotional context of an experience. However, this great scientific goal does not seem quite so marvelous when one asks the question: is the cost of eliminating memories or the emotional aspects of memory worth the benefit of reducing suffering? This question, forces an individual to think of the value of his or her memory, the value of his or her emotions, and the problems that may arise for society if a treatment is found. Nothing is as simple

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as it seems. It is important to not accept things as right or wrong simply because one opinion is the general consensus. Instead, each person must ask his or her self tough questions and form his or her own answers to those questions. It is through the thought processes that one takes in answering such questions that truly informs the individual. Although the development of a treatment for PTSD is not a single person's decision, the administration of a treatment does require one's consent. Before consenting to a memory altering treatment, each person with the potential of developing PTSD must think of the consequences, both good and bad, that the treatment may have. As I move forward beyond Regis, I will continue to ask hard questions, to search for the answers to these questions, and ultimately to find meaning in my work and life.

Along with the continuation of asking hard questions, I will also continue to take action towards the reduction of suffering. It is through action that a person can find his or her meaning in life. Regardless of any trauma one has endured or any hardships that lie ahead, it is crucial for an individual to be proactive and reactive. Each person must take action by pursuing the achievement he or she wishes to see and striving for his or her own personal growth. Regardless of one's beliefs on the value of suffering, it is true that today

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is not yesterday, and every day that we live, we move closer to death. One must not live in the past or for the future; we must all live for today. Ultimately, by living in the moment and asking the hard questions that inform one's life, one will find his or her meaning in the world, which is the art of Magis.

Magis, Latin for *more*, is the Jesuit concept of living a life for the greater glory of God and continually striving to improve the world. The needs of the world become visible only through straining to see the way that the world truly is. One must strain to see the injustices that lie in front of them and the suffering that affects the lives of our friends, families, and fellow persons. About 7 billion people live on Earth, and each person has his or her own hardships and experiences with suffering. If you cannot imagine the quantity of 7 billion, simply multiply yourself as well as all your qualities, attributes, experiences, and imperfections by 7,000,000,000. The world is a massive place, and much of the time the individual gets lost in the expansiveness of the world. This is exemplified when Dillard cites Stalin as saying, "One death is a tragedy; a million deaths are a statistic" (2000). All too often, suffering is generalized into a common phenomenon. If one is truly looking to live out the Magis, he or she will seek to find and make just the injustices in the world, and suffering will not

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simply become a statistic. Although one is not able to redeem the entire world, no person is free to take no part in it. Each person must find his or her purpose by searching for the Magis every day and redeeming his or her own speck of the world.

With the conclusion of this thesis, I near the end of my time at Regis University, and as I prepare to leave Regis, I am determined to remain passionate about the value of learning, the pursuit of knowledge, and the belief that asking hard questions leads to greater understanding. These are the things that Regis has instilled in me, and the reason that I chose to write a thesis that would test all facets of my intellect. I have also chosen this thesis topic because I found an injustice in world and hoped to redeem a small part of the injustice. Throughout this thesis, I have attempted to play a small role by creating awareness of PTSD and searching for a treatment. Through this thesis project, I have searched for the Magis, and I hope that this work has managed to redeem a speck of the world. Regardless of where life leads me after graduation, I will continue to search for the Magis, to redeem small specks of the world, and to run with full speed towards excellence. Furthermore, I promise to never lose sight of the man I have

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become as a product of my experiences, my education, my relationships, and this thesis project.

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