ATLANTIC GUARDIAN

The Forgotten Ones

Abandoned and broken our Veterans are facing a burgeoning health crisis

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Veterans are in the grips of a national health crisis from toxic stress induced brain injury. Despite billions spent by the federal government, rates of suicide, homelessness and substance abuse either rise or stay flat in the Veteran population. In this paper we will briefly discuss the pathogenesis causing this, and we will also discuss integrative medical therapies to combat this epic problem gripping our nation's service men and women.

The United States is committed to a prolonged state of armed conflict, which has created a crisis for Veterans in America. The crucial issue of mental health care for veterans is more important than ever before due to the considerable number of veterans returning from combat missions who have experienced episodes of PTSD and other mental health conditions. More than 1.5 million of the 5.5 million veterans seen in VA hospitals had a mental health diagnosis in 2016.[i] This represents about a 31% increase since 2004. Diagnosis of PTSD is on the rise, as the changing nature of warfare increases the chance for injuries that affect mental health and as our veterans face significant challenges upon returning home.[ii] The potential negative effects of mental health issues, such as homelessness and suicide, affect the more than 107,000 veterans who are homeless on any given night. Alarming numbers of veterans die by suicide each day, which makes the response to veteran mental health needs more urgent with each passing day.[iii]

Schoembaum and Kessler [iv] examined common mental health disorders among Army participants and whether the disorder developed prior to entering the Army. They found in their landmark study that the most common disorders for Army participants was ADHD and intermittent explosive disorders, both are mental health predictors for suicide and accidental death based upon the results from the Army Study to Assess Risk and Resilience in Service members (Army STARRS). The prevalence of the theses disorders is higher among Army Soldiers compared to civilian populations of the same age and sex.

This is an excerpt from the Office of the Under Secretary of Defense letter to Senate Oversite Committee 2016 - **"*Prospective members of the Armed Forces are screened at the time of accession for both currently present, and histories of, physical and mental conditions that may be disqualifying for accession. The Department of Defense (DoD), specifically the United States Military Entrance Processing Command (USMEPCOM), has processes in place to conduct these screenings and to identify individuals who do not meet the standards outlined in Department of Defense Instruction (DoDI) 6130.03 "Medical Standards for Appointment, Enlistment, or Induction in the Military Services," dated April 28, 2010. Each of these screening steps in the Military Entrance Processing Station (MEPS) examination process is detailed in the Attachment of this report.*"**

"These Medical Standards require screening for learning, psychiatric, and behavioral issues inclusive with screenings for all physical systems (e.g., neck, eyes, spine) and other

***conditions (neurologic and sleep disorders). If, at the time of this screening, a physical or mental condition is identified that may be disqualifying, the prospective member can be referred for additional assessment by a medical specialist consultant prior to a final medical qualification decision being made by USMEPCOM. Not all applicants are referred. If the MEPS provider has enough information to make the medical qualification decision, a consult is not necessary. The consultants never make the qualification decision; they just provide medical information regarding the applicant, and the MEPS medical provider, as the DoD authority for this decision, can independently medically qualify or disqualify the applicant based on their clinical judgment*"**

This passage clearly states MEPS screens military recruits for mental health disorders upon enlistment. Simply put the overwhelming incidence of **mental health injury** among Veterans is a direct result of their military experience.

The Numbers: The military employees over 1.3 million men and women. According to the Rand Corporation there have been a total of 1.4 million combat deployment years to Iraq and Afghanistan from 2001 to 2018. This includes individuals with multiple deployments. According to War-Dog.Org there was 1.6 million combat deployment years to Vietnam when the Department of defense had 2.7 million Active Duty Members.

Economists Stiglitz and Bilmes state in their book 'The Three Trillion Dollar War' gross estimates of treating veterans with PTSD will reach over 950 billion USD exceeding the total cost of war. Stiglitz, a Nobel Laurate in Economics, explains in his book that Veteran Administration's (VA) estimates are grossly underestimated due to both an increase in VA claims since 2005, and the inability of the VA to fore-see the full spectrum of medical conditions the Veterans suffer as a bi-product of PTSD.

Stiglitz further states "*Historically, the cost of caring for war veterans rises for several decades and peaks 30 to 40 years or more after a conflict. This will be especially true for veterans of the current wars, who are already utilizing VA medical services and applying for disability benefits at much higher rates than in previous wars*."

- Evidence from previous wars shows that the most significant long-term budgetary cost of war is providing medical care to those who have served, and paying disability compensation, pensions, and other benefits to eligible veterans[v]

- Studies show that PTSD sufferers are at a higher risk for heart disease, RA, bronchitis, asthma, liver, and peripheral arterial disease. [vi]
- Veterans are 200% more likely to be diagnosed with a disease within five years from returning from deployment. [vii]

Statistics according to Watson Institute of International and Public affairs

- The cost of caring for war veterans peaks 30 to 40 years after a conflict, but there are no provisions to cover these future obligations in current wars.
- Future medical and disability costs for Iraq and Afghanistan veterans will total between $600 billion and $1 trillion.
- Uncompensated costs include loss of income for injured veterans and their family caregivers and diminished quality of life.

The Department of Urban and Housing Development (HUD)

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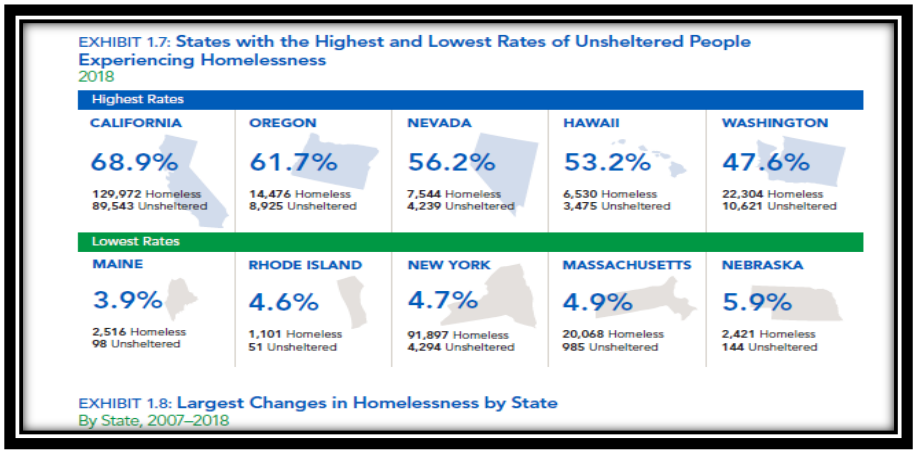
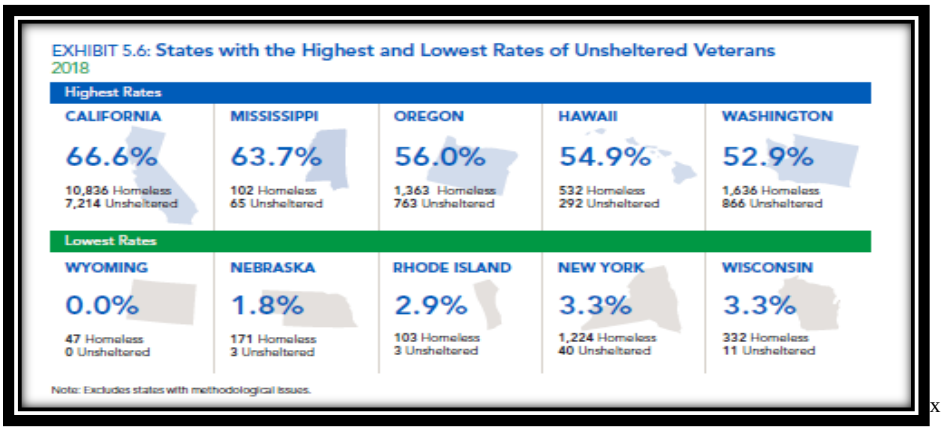


1. HUD recently published numbers over the past decade state Veterans make up between 12 to 19 percent of the homeless population despite making up less than seven percent of the overall population. Take into account that 33 percent of total homeless are children living with their parents. Put another way one in three adult homeless are Veterans.
2. A majority (55%) of Veterans experiencing sheltered homelessness had a disability. Among Veterans experiencing homelessness who received health care services from the VA, more than one in four (28%) received diagnoses of chronic medical conditions, more than one in four (28%) received a diagnosis of depression, one in eight (13%) received a diagnosis of

PTSD, about one in five (19%) received a diagnosis of alcohol abuse, and about one in five (20%) received a diagnosis of drug abuse.[ix] There is not very good data currently available regarding the health services Veterans receive outside of the VA system.

- Over 968,000 veterans lived in poverty in the last year
- 20,000 veterans with government sponsored mortgages lost their homes in 2010
- 76% of homeless veterans experience alcohol, drug, or mental health issues
- 30.2% of veterans ages 18-24 are unemployed
- 89% received an honorable discharge
- 67% served 3 years or more
- 47% are Vietnam veterans
- 15% served before Vietnam
- 5.5% are Iraq and Afghanistan veterans



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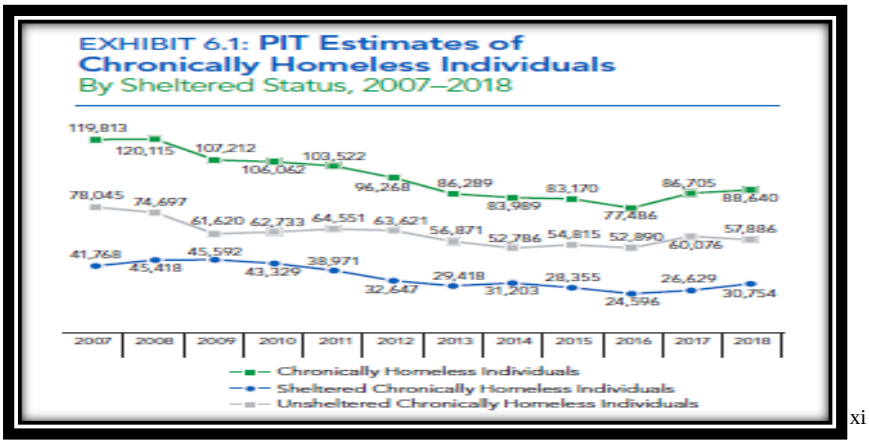

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National Institute of Health (NIH)

- NIH published a study in 2016 stating that 40% of Veterans will suffer a Substance Abuse Disorder (SUD) with-in their lifetime, compared to the civilian population rates of 10%
- Veteran populations demonstrates that, in comparison to the general population, Veterans are at increased risk for developing both PTSD and SUDs, and that severity of combat exposure is directly linked to risk for development and chronicity of PTSD symptoms[xii]
- Veterans comprise 20% of national suicides, with approximately three out of five veterans who died by suicide being diagnosed with a mental health condition.
- Veterans are 50% more likely to commit suicide than people who have never served in the military
- According to the report, suicide rates among veterans age 18 to 34 have been swelling steadily for more than 10 years, jumping 10% from 2015 to 2016 alone.
- National Suicide Data Report reports the rate for those young veterans increased to 45 suicide deaths per 100,000 populations in 2016, up from 40.4 in 2015, even as the overall veteran suicide rate decreased slightly.

This is nothing less than distressing; these numbers speak to the inadequacy in current treatment and neglect to those who have sacrificed. According to a study conducted at NIH only 30% of Veterans are enrolled in Veteran Administration care and there report finds disparities in that care given[xiii]. Despite the Veterans administration efforts rates of suicide, substance abuse and veteran homelessness continue to stay flat or rise. This is of significant importance to the state of California due to the size of the Veteran population residing there.

The Problem: An important factor of diagnosis and treatment in Veteran Populations, are the physiological and functional changes of the brain and endocrine system due to Repeated and Prolong Stressful Environments (RPSE). The research community has recently coined the phrase 'Chronic unpredictable mild stress (CUMS)' to refer to states of prolonged stress when used in animal models. It is now being widely accepted in the field of neuroscience research that exposure to prolonged stressful environments cause structural changes to the brain and reduces vital hormones needed to regulate healthy states. RPSEs results in pathological changes in brain tissue and the endocrine system resulting in brain, endocrine and immunological dysregulation.

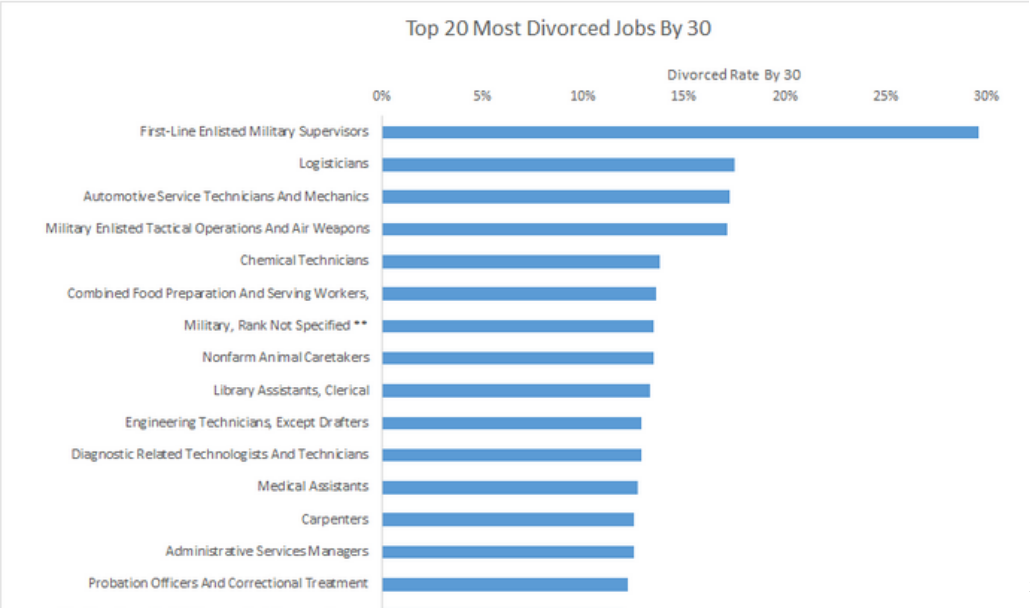
Symptoms include

- Decreased cognition
- Depressed motor function
- Depressive symptoms
- Anxiety
- Increased need to self-medicate
- Prone to injury and sickness
- Chronic Fatigue

The reason there is a Veteran Mental Health Crisis is because Veterans are overwhelmingly diagnosed with Mood and Anxiety disorders due to Trauma, and what is being overlooked is brain damage due toxic effects of stress over time. Being a member of the US military is burdened with many stressors that go unrecognized. Such as extended time periods away from family, long hours on night schedules and stressful training environments. Most US military personnel will suffer some type of injury in their career, with the army citing 2500 injuries for every 1000 soldiers.[xiv] U.S. Military Personnel are expected to maintain professional

advancement, with often limited advancement opportunities, resulting in automatic discharge if they fail to advance. This is referred to as higher tenure. According to the Census Bureau there are 23000 active duty members living on SNAP benefits formerly known as food stamps.

Active Duty Military Members are not the only ones who are impacted by the demands of the military. Depicted below Military Supervisors have the highest divorce rates among any career, according to PUMS data published in a 2015 report by the U.S Census Bureau.



[xv]

This is just a fraction of the stress active duty personnel live with, not including deployments to combat zones, which are often six months to a year in duration. Although, each of the stressors individually may not cause the toxic effects of stress, in combination they create a cascading additive effect.

The adult as well as developing brain possesses a remarkable ability to show structural and functional plasticity in response to stressful and other experiences, including neuronal replacement, dendritic remodeling and synapse turnover. Stress can cause an imbalance of neural circuitry sub serving cognition, decision making, anxiety and mood that can increase or decrease expression of those behaviors and behavioral states. This imbalance, in turn, affects systemic physiology via neuroendocrine, autonomic, immune and metabolic mediators. In the short term, these changes may be adaptive; but, if the threat passes and the behavioral state persists along with the changes in neural circuitry resulting in pathology. When exposed to moderate to high

stress our bodies have the ability to maintain healthy states for two to four weeks. Once the body's resources are depleted our homeostatic process begins to pull resources from other vital systems of the body, for example our immune system. This is why we are prone to illness after stressful events. We no longer have the ability to build healthy tissue but instead begin a cycle of healthy tissue destruction known as catabolism.[xvi]

"Every stress leaves an indelible scar, and the organism pays for its survival after a stressful situation by becoming a little older." - Hans Selye, MD, PhD

General Adaption Syndrome (GAS) was coined by a Hungarian endocrinologist Hans Seyle describing his observations of the human body to stress. In Dr. Seyle's GAS model, stressors will lead to three stages of physiological response if exposed to that stressor over a period of time. The first stage is ***Alarm*** the body reacts with a "fight-or-flight" response and the sympathetic nervous system is stimulated as the body's resources are mobilized to meet the threat or danger. The second stage is ***Resistance*** in which the body compensates as the parasympathetic system attempts to return back to a homeostatic state. Lastly, ***Exhaustion*** this is when the stressors go beyond the body's capacity to compensate.[xvii] Stress can also be classified as the following:

- "Good stress" refers to the experience of rising to a challenge, taking a risk and feeling rewarded by an often positive outcome. A related term is "eustress." Good self-esteem and good impulse control and decision making capability, all functions of a healthy architecture of the brain, are important! Even adverse outcomes can be "growth experiences" for individuals with such positive, adaptive characteristics that promote resilience in the face of adversity.[xviii]
- "Tolerable stress" refers to those situations where bad things happen, but the individual with healthy brain architecture is able to cope, often with the support of family, friends and other individuals. These adverse outcomes can be "growth experiences" for individuals with such positive, adaptive characteristics and support systems that promote resilience. Here, "distress" refers to the uncomfortable feeling related to the nature of the stressor and the degree to which the individual feels a lack of ability to influence or control the stressor.[xix]

- "Toxic stress" refers to the situation in which bad things happen to an individual who has limited support and who may also have brain architecture that reflects effects of adverse early life events that have impaired the development of good impulse control and judgment and adequate self-esteem. Here, the degree and/or duration of "distress" may be greater. With toxic stress, the inability to cope is likely to have adverse effects on behavior and physiology, and this will result in a higher degree of allostatic overload.[xx]

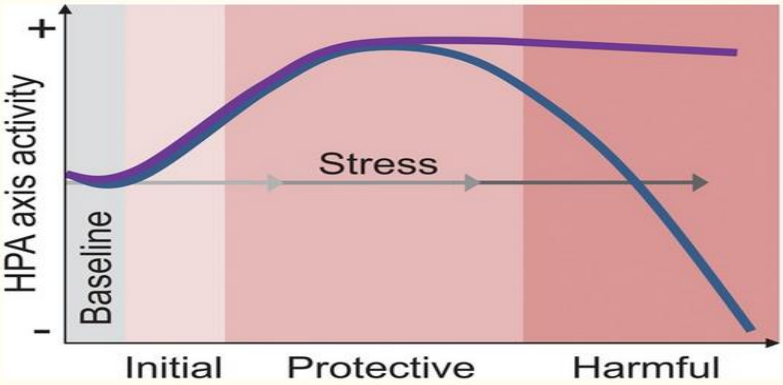


Figure 3.

Two HPA axis-based models of stress. Selye's (1936) general adaptation syndrome proposed that the depletion of neuroendocrine factors with persistent stress makes the body susceptible to diseases (blue line). In contrast, current views hypothesize that abnormally elevated and/or long-lasting neuroendocrine activity causes harm to the body (purple line). The three gray-gradient arrows represent mild, moderate, and severe stress.

[xxi]

1. **Stress is associated with a greater risk for mental health problems including reduced gray matter volume (GMV) and density in a number of brain regions**. Under stress, brain regions such as the hippocampus, amygdala, and prefrontal cortex undergo structural remodeling, which alters behavioral and physiological responses. The decrease in prefrontal cortex grey matter is found to cause a decrease in cognitive and executive function. Arnsten, Lupien and Ansell found the mechanisms through which stress may affect GMV, including loss of neurons, decreased dendritic branching, spine density, and decreased neurogenesis. [xxii] Research published in JAMA Psychiatry found similar Gray Matter volumes in children with conduct problems, which is often associated with childhood abuse and neglect.[xxiii]

(Tomoda et al., 2009) conducted a study of 1,455, twenty-two year old men, plus or minus two and half years, looking at the effects of harsh corporal punishment on prefrontal cortex development in this population. Using t1 weighted MRI they evaluated densities in the front and

mid brain. Their results showed total Grey Matter Volume (GMV) was reduced by 20%. Their findings also associated decreased GMV with depression, aggression and addictive behavior.[xxiv]

(Gueze, Elbert and Westenberg, 2008) conducted a study with using magnetic resonance imaging to evaluate the prefrontal cortex in Veterans with PTSD. Twenty-five male veterans with PTSD and twenty-five male veterans without PTSD matched for age, year and region of deployment were recruited. All the subjects were scanned using MRI. Subjects' brains were aligned using cortex-based alignment in a region of interest based approach. Individual cortical thickness maps were calculated from the MR images. Regions of interest examined included the bilateral superior frontal gyri, bilateral middle frontal gyri, bilateral inferior frontal gyri, bilateral superior temporal gyri, and bilateral middle temporal gyri. In a large number of patients and controls, IQ scores and memory scores were also obtained. Individual cortical thickness maps were calculated from the MR images.

Veterans with PTSD revealed reduced cortical thickness in the bilateral superior and middle frontal gyri, the left inferior frontal gyrus, and the left superior temporal gyrus. Veterans with PTSD performed significantly worse on memory measures compared to control veterans. Cortical thickness correlated with memory measures in the veterans without PTSD, but not in the veterans with PTSD. Cortical thinning in these regions may thus correspond to functional abnormalities observed in patients with PTSD. [xxv]

The anterior cingulate cortex (ACC) and insula have been implicated in both autonomic responses to emotional stressor and homeostatic processes, which may contribute to cardiovascular dysfunction in combat veteran populations. Current research suggests that individuals with PTSD exhibit smaller anterior insula volume compared to those without PTSD. [xxvi] This region of the brain coordinates emotional regulation and assists in autonomic regulation, including cardiovascular response to stress. The study found that the mid-region of the brain densities did in fact correlate to poor cardiovascular health.[xxvii]

2. **Excessive Stress causes inflammatory induced brain injury.** Depressed patients have been found to have higher levels of pro-inflammatory cytokines, acute phase proteins, chemokines and cellular adhesion molecules. In addition, therapeutic administration of the cytokine interferon-α leads to depression in up to 50% of all patients it is administered to. Moreover, pro-inflammatory cytokines have been found to interact with many of the pathophysiological domains that characterize depression, including neurotransmitter metabolism, neuroendocrine function,

synaptic plasticity and behavior. Stress, which can precipitate depression, can also promote inflammatory responses through effects on sympathetic and parasympathetic nervous system pathways.[xxviii]

Excitatory amino acids, particularly glutamate, play a key role in structural as well as functional changes in the brain since glutamate is the major excitatory transmitter, while, at the same time, excess glutamate causes damage and inflammation.[xxix] Initial studies of restraint stress which, when chronic, causes shrinkage of apical dendrites of hippocampal CA3 neurons[xxx], showed that acute restraint stress elevates extracellular glutamate levels via a process that is blocked in adrenalectomized animals, implicating the adrenal cortex.[xxxi] Corticosterone acts directly via membrane associated mineralo-corticoid receptors (MR) and glucocorticoid response (GR) to cause glutamate release. [xxxii], [xxxiii], [xxxiv]

There is a point of unregulated glutamate excitation that triggers irreversible changes resulting in amyloid beta toxicity and dementia. Amyloid beta formation is seen in people with Alzheimer's disease resulting in the symptoms of dementia.[xxxv]

Abnormal Immune regulation secondary to inflammatory states results mitochondrial failure. Mitochondria are the power factories of the cell creating adenosine triphosphate (ATP) needed for proper cellular function and metabolism. ATP is the cellular source of energy and with-out it Cells will function abnormally. Probably the most important role of the mitochondria organelle is to provide a supply of energy so that transcription takes place. Transcription is the process of creating the building blocks so that cell can divide, grow and regulate its size. In states of allostatic/toxic stress a massive demand for energy is placed on the mitochondria. Cortisol acting as a stress hormone signals the mitochondria to increase in energy production on an exponential scale. In prolong states of energy demand; the cellular matrix begins to breakdown due to oxidative stress, increased heat production in its membranes and a decrease in anabolic growth signaling. With-out ample supplies of energy cells cannot divide or repair.[xxxvi]

Abnormal mitochondrial function secondary to stress metabolism are linked to poor cognitive function, increased insulin production and abnormal regulation of the circadian rhythm. In times of prolonged stress the mitochondria also changes shape, in-order to adapt to different metabolites, these changes are thought to account for the metabolic syndrome associated with prolong exposure to glucocorticoids or cortisol.[xxxvii] This may be a factor in the decrease in frontal lobe grey matter, hippocampus, and amygdala densities

3. **<u>Toxic stress results in greater turnover of brain signaling neurotransmitters</u>**: Increased neurotransmitter turn-over including serotonin, dopamine and norepinephrine due to both insulin resistances caused by excessive cortisol release and reduced levels of neurotransmitters due to enzymes that increase uptake and decrease efficacy.[xxxviii]

The amygdala is an almond-shaped nucleus located deep and medially within the temporal lobe and is thought to play a crucial role in the regulation of emotional processes. GABAergic neurotransmission inhibits the amygdala and prevents us from generating inappropriate emotional and behavioral responses. Stress and sleep deprivation cause the reduction of the GABAergic interneuronal network and the development of neuropsychological diseases.[xxxix]

GABA is the principal neurotransmitter mediating neural inhibition in the brain. GABAergic neurons are present throughout all levels of the neuro-axis, represent between 20 and 40% of all neurons depending on brain region, and are known to balance and fine tune excitatory neurotransmission of various neuronal systems including the monoaminergic and cholinergic projections to the forebrain. GABA exerts its effects by activation of two entirely different classes of receptors, the ionotropic $GABA_A$ receptors ($GABA_A$Rs) and the metabotropic $GABA_B$Rs. $GABA_A$Rs are known as key control elements of anxiety state based on the potent anxiolytic activity of benzodiazepines (BZs) that act as positive allosteric modulators of a major subset of $GABA_A$Rs.

Accumulating evidence described below points to marked alterations in $GABA_A$R signaling in both anxiety and mood disorders. $GABA_B$Rs are members of the G-protein coupled receptor family and they have been recently implicated in affective disorders based on altered anxiety- and depression-related behavioral measures in mice subject to pharmacological and genetic manipulations of these receptors. $GABA_B$(1) and $GABA_B$(2)R KO mice show behavior indicative of increased anxiety combined with an antidepressant phenotype.[xl], [xli]

4. **<u>Chronic Toxic Stress causes a dysregulation of our hormones and immune system beginning in the hypothalamus</u>.** A large body of research has shown that the interaction of the hippocampus and the hypothalamic-pituitary-adrenal (HPA) axis might explain the onset of various illnesses.[xlii] The HPA axis has traditionally been regarded as the body's stress tolerance and energy regulation system. Its hyperactivation is associated with excessive release of stress hormones (e.g. glucocorticoid, cortisol) and subsequently results in various health problems.[xliii]

Meanwhile, the hippocampus activity has been suggested to exert a tonic inhibitory influence on the activation of HPA axis and subsequently decrease glucocorticoid secretion, and promote more efficient regulation of the HPA axis to ultimately promote physical health.

In a study published in NCBI looking at inflammatory markers and cortisol levels of Wildland Firefighters, they found a direct correlation between excess cortisol due to stress and the inflammatory markers interleukins and cytokines.[xliv]

First, sympathetic fibers descend from the brain into both primary (bone marrow and thymus) and secondary (spleen and lymph nodes) lymphoid tissues. [xlv] Sympathetic fibers are intended to prepare the body for fight or flight. The sympathetic fibers located in bone marrow and thymus redirect resources, specifically energy transfer. These fibers can release a wide variety of substances that influence immune responses by binding to receptors on white blood cells. Simply put it shuts down production of the immune system to redistribute resources to produce energy to either fight or flee. Second, the hypothalamic–pituitary–adrenal axis, the sympathetic–adrenal–medullary axis, and the hypothalamic–pituitary–ovarian axis secrete the adrenal hormones epinephrine, norepinephrine, and cortisol; the pituitary hormones prolactin and growth hormone; and the brain peptides melatonin, β-endorphin, and enkephalin. These substances bind to specific receptors on white blood cells and have diverse regulatory effects on their distribution and function.[xlvi] Third, people's efforts to manage the demands of stressful experience sometimes lead them to engage in behaviors—such as alcohol use or changes in sleeping patterns—that also could modify immune system processes.[xlvii]

The most chronic stressors were associated with the most global immunosuppression, as they were associated with reliable decreases in almost all functional immune measures examined. Increasing stressor duration, therefore, resulted in a shift from potentially adaptive changes to potentially detrimental changes, initially in cellular immunity and then in immune function more broadly. It is important to recognize that although the effects of chronic stressors may be due to their duration, the most chronic stressors were associated with changes in identity or social roles (e.g., acquiring the role of caregiver or refugee or losing the role of employee). These chronic stressors may also be more persistent, that is, constantly rather than intermittently present.

5. **Chronic Toxic Stress induces long lasting changes in the part of the brain causing feelings of negative self-esteem, depression, sleep abnormalities, inappropriate behavioral response and impulse control**. In a recent study conducted in China, (Huanhua et al., 2013) discovered

the link between hippocampus density and self-esteem.[xlviii] In the presence of Chronic Toxic Stress the hippocampus undergoes drastic changes. The hippocampus is part of the limbic system which includes the hypothalamus and the amygdala. The hippocampus is located in the middle of the brain and is responsible for emotional regulation, memory consolidation in sleep, and behavioral inhibition. Some researchers believe damage, or dysregulation of the hippocampus leads to Substance Abuse Disorders seen in Veteran populations. This suggests that the hippocampus is a key node in the neural circuit underlying the link between self-esteem and physical health. In the face of stressful situations, the HPA axis, the autonomic nervous system, and the cardiovascular, metabolic, and immune systems interact with each other to achieve allostasis (adaptation) in the short term and lead to allostatic load ("the wear and tear on the body") in the long term.[xlix] Prolonged and/or traumatic stressors have also been shown to cause morphological changes in the hippocampus. In particular, and with significant clinical implications, human brain imaging studies have reported that PTSD patients had smaller hippocampal volume, which correlated with deficits in verbal memory. [l] More recent studies have found that functional neurons are replaced with the lipid supporting structures of the brain known as myelin. These changes in the hippocampus cause feelings of negative self-esteem, depression, sleep abnormalities, inappropriate behavioral response and impulse control.

Bansar Duman published evidence suggests that chronic stress has significant effects on glial cell function. Several studies have demonstrated decreases in the expression of glial fibrillary acid protein (GFAP) and in the number of GFAP-expressing glial cells in the hippocampus and PFC following exposure to chronic stress.[li]

In an article publish in psychology today, author Bergland, C references new research carried out at UC Berkley - "*researchers found that chronic stress made stem cells in the hippocampus mature into another type of glial cell called an* ***oligodendrocyte****, which produces the myelin that sheaths nerve cells. This finding suggests a key role for oligodendrocytes in long-term, and perhaps permanent, changes in the brain that could set the stage for later mental problems. Chronic stress decreases the number of stem cells that mature into neurons, which might provide an explanation for how it also affects learning and memory, according to the researchers*."

6. **Toxic Stress and toxic stress related brain injury causes abnormal circuitry relays in the brain.** (Wuingen et al., 2004) showed in animal models that combat stress induced a persistent reduction in functional connectivity between the midbrain and prefrontal cortex. Their results

demonstrate that combat stress has adverse effects on the human mesofrontal circuit and suggests that these alterations are partially reversible.[lii] The amygdala is a section of the brain that is responsible for detecting fear and preparing for emergency events. There are two amygdalae per person normally, with one amygdala on each side of the brain. They are thought to be a part of the limbic system within the brain, which is responsible for emotions, survival instincts, and memory.[liii] Research published in BIOL Psychiatry states "*results of our study provide clear evidence of an association between a smaller amygdala volume and PTSD. The lack of correlation between trauma load or illness chronicity and amygdala volume suggests that a smaller amygdala represents a vulnerability to developing PTSD or the lack of a dose-response relationship with amygdala volume.*"[liv] Not only does stress cause a decrease in amygdala size but creates abnormal circuit connection between it and the frontal cortex.

(Park, A et al., 2015) discovered an association with disrupted functional connectivity between the amygdala and medial prefrontal cortex (mPFC), which results in higher levels of aggressive behavior and attention problems.[lv] Remember we discussed in the opening of this paper, (Schoembaum and Kessler, 2011) found in their landmark study that the most common disorders for Army participants was ADHD and intermittent explosive disorders. [lvi]

7. **The effects of Chronic Toxic Stress alter the circadian rhythm preventing restorative sleep patterns long term**. Humans possess a molecular circadian clock present in most cells of the body. The hypothalamic-pituitary-adrenal (HPA axis) endocrine access axis assists in this process by releasing cortisol in early morning bursts, in response to light, because of its waking properties. The HPA axis also regulates the body's response to acute and chronic stress. The HPA axis also plays a major role in regulation of our immune system.

Our circadian rhythms are synchronized to environmental cues which are controlled in a region of the brain known as hypothalamic suprachiasmatic nuclei (SCN). When visible light hits our retinas in the morning it causes a neuro-endocrine response results in the release of cortisol from the adrenal glands. As the day progresses to evening certain transcription proteins build inhibiting the wake response. Once the body registers low light and subthreshold of cortisone it triggers chemicals such as melatonin to produce states of sleep induction. This is all dependent on a very fine balance of release of both glucocorticoids and adrenal hormones referred to as catecholamines.

During prolonged periods of chronic stress our neuro-endocrine system causes shifts in both tissue and chemicals which inhibit restorative sleep long-term. Secondly the disorders PTSD and Depression cause fragment sleep reducing time needed in each stage of sleep.

There is evidence that the absence of sleep increases brain oxidative stress.[lvii] Oxidative stress in the brain has shown to destroy lipid membranes of nerve tissue, produce toxic protein metabolites found in the CSF, and also cause degenerative inflammatory response in the brain. Now, take into account sleep disturbances from conditions such as PTSD and TBI and you have the makings of a population suffering from chronic sleep deprivation.

According to John Hopkins Medicine risks of sleep deprivation are

1. weight gain and metabolic syndrome due to increase of ghrelin
2. 65% increased risk of developing diabetes
3. increased blood pressure
4. weakened immune system
5. 48% more likely to develop heart disease
6. 33% increased risk of dementia
7. 36% increase risk of colorectal cancer

Recent meta-analysis found that, among the highly variable alterations of sleep in PTSD compared to control groups, increased stage 1 NREM sleep, decreased slow wave sleep (SWS), and increased average number of rapid eye movements per minute in REM sleep (REM sleep density) were the most consistent abnormalities across studies.[lviii] Additional abnormalities expressed by subgroups of PTSD patients included shorter total sleep time (TST), increased sleep onset latency, reduced stage 2 NREM sleep, and increased REM sleep as percent of TST.

Polysomnographic studies have also shown that EEG spectral power at delta frequencies is significantly decreased in PTSD patients. These abnormalities are consistent with an underlying hyperarousal in PTSD that lightens sleep, prevents deeper, more restorative sleep stages, and alters the distinct physiology of REM sleep. Evidence that PTSD may influence the quality versus absolute quantity of REM includes not only greater REM density but the fact that some studies have shown greater percent REM in PTSD.

A new study of young U.S. veterans shows that the probability of having a high risk of obstructive sleep apnea (OSA) increased with increasing severity of post-traumatic stress disorder (PTSD) symptoms. The study involved 195 Iraq and Afghanistan veterans who visited a VA outpatient PTSD clinic for evaluation. Results show that 69.2 percent of participants had a high risk for sleep apnea, and this risk increased with PTSD symptom severity. Every clinically significant increase in PTSD symptom severity was associated with a 40 percent increase in the probability of screening as high risk for sleep apnea. Sleep apnea is known to be a long-term risk for dementia, hypertension and cardiovascular events.

Sleep disruption may lead to fatigue, executive deficits, mood dysregulation, and psychosocial impairments, all of which may degrade psychological resilience and exacerbate symptoms.[lix]

8. **Chronic Toxic Stress induces epigenetic changes of the brain altering the brain architect.**

Epigenetics is a process of DNA modifications that does not change the DNA sequence, but can affect gene activity. Epigenetic changes can help determine whether genes are turned on or off and can influence the production of proteins in certain cells, ensuring that only necessary proteins are produced. A common type of epigenetic modification is called methylation. Methylation involves attaching small molecules called methyl groups, each consisting of one carbon atom and three hydrogen atoms, to segments of DNA. When methyl groups are added to a particular gene, that gene is turned off or silenced, and no protein is produced from that gene.[lx]

A group led by Drs. James B. Potash and Gary S. Wand at the Johns Hopkins University School of Medicine set out to investigate how glucocorticoids affect genes central to the HPA axis. They hypothesized that the hormones may affect the HPA axis through epigenetic modifications—changes to DNA that don't alter sequences but influence gene expression. The researchers added corticosterone—the major hormone that mice produce in stressful situations—to their drinking water for 4 weeks. After exposure, and again after a 4-week recovery period without corticosterone, the scientists tested the mice for behavioral and physiological changes. They examined the expression levels of 5 HPA axis genes in the hippocampus, hypothalamus and blood. They also tested the genes' methylation levels—a common epigenetic modification that affects gene expression. The study was funded by grants from NIH's National Institute on Alcohol Abuse and Alcoholism (NIAAA), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and National Institute of Mental Health (NIMH).

Genome-wide methylation studies support the existence of epigenetic differences between trauma-exposed individuals with PTSD compared to psychiatrically healthy controls, with cross-sectional differences in DNA methylation observed in cohorts from Atlanta.[lxi] These studies have shown that epigenetic differences were able to differentiate those who have developed PTSD compared to those who did not. Later studies from longitudinal cohorts of US military personnel exposed to combat-trauma further suggested significant differences in global methylation in PTSD patients relative to controls,[lxii] particularly in genes involved in immune [lxiii] [lxiv] and nervous system function.[lxv]

A study conducted at the Veterans Affairs, Fishberg Department of Neuro Science, Division of Molecular Neuro-Imaging and Neuropathy, New York State Psychiatric Institute recently conducted research looking at DNA methylation in the prefrontal cortex of suicide patients. The study shows increased age-related DNA methylation perturbations in prefrontal cortex in major depression suicide compared with non-psychiatric controls.[lxvi] Note the methylation process depicted in this study was not from associated trauma, but rather age related DNA methylation, for one can hypothesis similar pathological processes.

9. **Comorbid conditions potentiating the Stress Induced Brain Injury**: As a result improved acute medical and surgical care in the field, veterans of recent wars have survived serious head injuries in greater numbers than ever before. In a survey of Operation Iraqi Freedom veterans from two brigades (Hoge et al. 2008), 15% had sustained a traumatic brain injury (TBI) either with loss of consciousness (LOS) or change in mental status. Using direct clinical evaluation of U.S. veterans of Iraq, Terrio et al. found 22.8% had suffered TBI, although most were mild.

There is a high prevalence and exposure risk to concussive forces while on active duty. In a recent article published in Task and Purpose on May 01, 2018 they discuss brain injury when using shoulder fired weapons which is commonly used with most ground forces. The article quotes recent research published by Center for New American Security (CNAS). *"[Department of Defense] studies have demonstrated that some service members experience cognitive deficits in delayed verbal memory, visual-spatial memory, and executive function after firing heavy weapon*" The article further states "*Service members risk brain damage when operating shoulder-fired heavy weapons like the AT4, LAW, and Carl Gustaf recoilless rifle, according to a new report by the CNAS.*"

Following traumatic experiences such as MTBI, psychological disturbances, such as post-traumatic stress-related symptoms and post-traumatic stress disorder (PTSD), can occur. Diagnosis of PTSD comprises a combination of intrusive, avoidance, and arousal symptoms. In a study conducted 6 months after MTBI, it was found that 20% of patients had developed PTSD[lxvii], whereas another study reported that 10% of patients exhibited 3 or more post-traumatic stress-related symptoms 1 year after MTBI.[lxviii] The quality of life of people who have experienced MTBI may further decrease.[lxix]

Many studies of post-concussion symptoms and complications after MTBI have follow-ups of 3 months, 6 months, or 1 year.[lxx lxxi lxxii]However, fewer studies have investigated the long-term effects and consequences several years after MTBI.[lxxiii lxxiv lxxv]Self-perceived limitations in psychosocial function with low levels of life satisfaction have been reported in patients 3 years after MTBI.[lxxvi] It has been shown that MTBI patients report significantly more post-concussion symptoms than control subjects 5–7 years after the injury. [lxxvii] MTBI can further result in sequelae that significantly reduce quality of life, even 10 years later.[lxxviii] In a follow-up study, patients with MTBI were evaluated 10 years after participating in a rehabilitation program, and life satisfaction had decreased in the intervention group, but not among the controls.[lxxix]

In a predominantly male veteran cohort, those diagnosed as having PTSD were at a nearly 2-fold-higher risk of developing dementia compared with those without PTSD. Between the years 2002 to 2009 a retrospective study was done looking at body mass index and rates of suicide within veterans, and findings showed 72% of men and 64% of women are either overweight or obese. [lxxx] It has also been mentioned in this review that Veterans diagnosed with mental health conditions are almost 200% more likely to suffer from other co-morbid conditions such as heart disease, diabetes and hypertension.

In summary we must address Veteran Mental Health not as a disorder but rather a global neuroendocrine syndrome caused by neurological insults, endocrine imbalance and mood disorders. Toxic stress in conjunction with traumatic events, and comorbid conditions such as TBI and substance abuse are causing pathological restructuring of the brain, and dysregulation of the endocrine and immune system. This syndrome must be addressed early and aggressively

through an integrative medical approach. If not properly addressed we will continue to watch as veterans commit suicide, abuse substances and suffer

The Answer - Integrative Medical Approach

1. Restore Neurological Metabolism (place for entheogens and psychedelics)
2. Restore Sleep through sleep medicine
3. Create environments conducive for Neuro & Angiogenesis (nurture and reconnecting through mirror neurons, and understanding of disease/education)
4. Restore Immune and Endocrine Function (hormone replacement therapy)
5. Enriching environments (brain stimulation both internal and externally to promote functionality)
6. Neurological Nutrition (diet specific for a neurotrophic environment)
7. Education and integration(Pt is part of the plan)

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