Effectiveness of Treatment of Veterans with PTSD: a Critical Review

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Abstract

Introduction: *PTSD impacts physiological, neurological, biochemical and epigenetic systems and is experienced largely unconsciously. Measures of treatment effectiveness vary widely but correspond to whether the modality of treatment creates an experience that is dominantly conscious or non-conscious.*

Objectives: *We evaluate the effectiveness of treatments for PTSD in the veteran population based on an analysis of published research.*

Methods: *A literature scan for PTSD, veterans and military personnel was conducted using CINAHL, PubMed, PILOT, Embase, ResearchGate, ScienceDirect, Wiley, PsycINFO, SpringerLink, ProQuest, PsycNET, MEDLINE, VA.com and Cochrane Library.*

Results: *1. Pathology is widely described but not related to diagnosis, treatment or measures of treatment efficacy. There are no descriptions of pathogenesis and nothing explicit about causation for veteran populations.*

2. Measures of treatment effectiveness are varied and inconsistent. Conscious therapeutic treatments like rational or cognitive behavioral therapy experience low efficacy, refractory response is 30-50%, and non-response is high.

3. Soldiers and veterans diagnosed with PTSD benefit less from psychotherapy than non-military populations. 78% of veterans are still in treatment after four years.

4. The research and treatment field is siloed by specialty and lacks a collaborative approach. Treatment of PTSD is hampered because veterans are reluctant to seek help. Also, PTSD is a multisystem response that is idiosyncratic and manifests in many ways.

Conclusions: *1. Treatment of PTSD could be more effective if it moved away from a symptom focused diagnostic process toward an ecology-based, systems approach that focuses on wellness. Collaboration across fields is therefore needed, along with effective comparison between studies against common criteria.*

2. Approaches that are unconscious such as Eye Movement Desensitization Reprocessing, Trauma informed Coaching, Virtual Reality and Reconsolidation of Traumatic Memory are highly efficacious but more sparsely studied when compared with Cognitive Behavioral Therapy and Exposure Therapy.

3. Treatments need to consider efficacy, balanced against refractory responses and risks of exacerbating the condition or harming the patient.

Keywords: soldier, VA, DVA, military, trauma, posttraumatic stress disorder, PTSD, PTS

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Introduction: trauma, response and diagnosis

PTSD is defined by behavioral signs and symptoms that have a pervasive pathology affecting the whole person; is a label used to describe a constellation of symptoms (Yehuda & McFarlane, 1995; van der Kolk et al., 2005):

- recurrent and intrusive disturbing recollections of the event – intrusive flashes of memory, vivid nightmares, illusions, hallucinations and dissociative episodes;
- intense psychological distress – including anxiety and panic;
- avoidance of stimuli – people, places and activities that trigger memories;
- collapsing inwardly – numbing, relational retreat, loss of interest, detachment, estrangement;
- intense physical reactions – racing heart, smothered breathing, feeling very upset, disembodiment;
- negative thoughts and emotions – fear, anger, guilt, isolation, shame and reduced affect (lack of love or diagnosis of alexithymia);
- increased or hyper-vigilance – poor sleep, high risk taking, looking for danger, easily startled, lashing out;
- inability to imagine the future – is not present to the current circumstance or propensity toward living in the past;
- psychogenic amnesia – failure to recall elements of the event.

PTSD is not a disease in the sense of being an illness with stable symptoms. It is a response, which may last a short or indefinite time. It is considered *Post* because the response is regarded as being related to a past event. However, the symptoms and recollection of the trauma are still current. It is *Traumatic* because an event, clearly distinguished from the challenges that normally occur in life by frequency (very rare), amplitude (severe) or length (e.g. long exposure to high pressure or duress) has occurred. It relates to *Stress* in that the individual has a very particular chain of stress responses (symptoms). It is widely described as a *Disorder*, although research shows that it is often a highly ordered response (Iribarren, 2005). There has been a strong effort in the military to drop the D from nomenclature to reduce stigmatization, labelling and medicalization (Smith & Whooley, 2015).

People possess, to one degree or another, the capacity to adapt to change, tolerate pain and cope with stress. Although most people can cope even with something out of the ordinary, such as divorce, financial crash or a car accident, many people do not cope when confronted by a traumatic event and their coping systems are overwhelmed, leading to decompensation (van der Kolk, 2005).

PTSD then is the failure to recover from an overwhelming situation (Creamer & McFarlane, 1999), yet much of the population (72%) are resilient to trauma and a further 20% have a response that peaks and returns to normal quickly (Skeffington, 2015). Everyone's perception of stressors is different, and each individual is resilient in their own way to a range of different things. Nobody's experience is the same.

Post-Traumatic Stress Disorder (PTSD) affects 8% of the civilian population (PTSD United, 2015) and 8% for the military at any one time (Zamorski & Boulos, 2013) – but the military population numbers rise and fall during deployment. The role of catastrophic thinking is posited to create higher prevalence in military personnel who have seen active service with veterans who have seen 4 combat stressors being 120% more likely to get PTSD than those who have had 2 (Seligman et al., 2017). After operational periods rates of PTSD rise: 12% of Gulf War veterans, 11-20% of Operation Enduring Freedom/ Operation Iraqi Freedom veterans, and 30% of Vietnam War veterans have PTSD (Veteran Affairs, 2015); although one large meta-study reports a range up to 60% (Fulton, 2019).

Method

A literature scan for PTSD, veterans and military personnel was conducted using CINAHL, PubMed, PILOT, Embase, ResearchGate, ScienceDirect, Wiley, PsycINFO, SpringerLink, ProQuest, PsycNET, MEDLINE, VA.com and Cochrane Library. Where a study stated that its results were not affected by demographics and/or were cross applicable to a military sample they were included. This resulted in 285 articles, from which those most directly related to treatment and effectiveness were used as the focus of this review (99 in total).

Diagnosis, treatment and ecology

Since the application of psychiatry in WWI for frontline treatment of shell shock, the field slowly aggregated around diagnosis and treatment. The diagnostic process for treatment is most commonly based on the Diagnostic Statistical Manual and is based on signs and symptoms.

In a study of 595 veterans with a clinical diagnosis of PTSD, high rates of false positive were determined by re-examining the veteran with the

Minnesota Multiphasic Personality Inventory-PTSD subscale (Cannon et al., 2010). PTSD is mistaken for a range of other issues and diagnosed instead of others:

Table 1. Common false-positive and false-negative diagnosis for PTSD (compiled from Cannon et al., 2010 and van der Kolk, 2014).

False-positives. Patients do not have PTSD but were diagnosed as PTSD	**False-negatives.** Patients have PTSD but were diagnosed with something else
Addiction and substance abuse Adult ADHD Depression Dissociative amnesia Dysthalmia Generalized anxiety disorder Paroxysmal nocturnal dyspnea Panic disorder Seasonal depression disorder Phobias	Adjustment disorder Acute stress disorder Antisocial personality disorder Brief psychotic disorder Clinical depression Epilepsy Malingering Obsessive compulsive disorder

At least one reason for poor diagnostic performance is that PTSD is comorbid with other mental health issues, and many diagnostic classifications share common pathologies (Richardson et al., 2017). Underlying causes include shared genetic and epigenetic expression (Lawford et al., 2006) and serotonin acting as a mediator for many related mental health issues: depression, anxiety, aggression and other disorders that are comorbid with PTSD (David et al., 1997).

To improve diagnostic accuracy, some practitioners offer prominent and overlapping clusters of symptoms as a strategy for structured, psychometric assessment. However, a phenomenologically based framework is just as likely to fail the patient as a symptom-based evaluation (Briere & Spinazzola, 2005).

Once a diagnosis takes place, very few veterans proceed through treatment of any kind. A 2010 Veteran Affairs (VA) study of 49,425 veterans who served between 2002 and 2008 and returned from Afghanistan with PTSD showed that only 9.5% attended 9 or more mental health sessions in the first year after diagnosis (Seal et al., 2010). Review of treatment responsiveness found military populations are poorer across every measure (Forbes et al., 2019), citing higher comorbidity of other mental illnesses as a contributing factor (Knowles et al., 2018).

The National Institutes of Mental Health (NIMH) rejected the symptomatology-based diagnosis advocated in the DSM-5 because it fails to give underlying causes, and offers too many competing alternatives (Insel, 2010). The NIMH moved to reviewing the human connectome (the neural pathways) using a systems-based approach instead.

Others in the field are also recognizing a systems-based approach, with Forbes et al. (2019) noting that "the onset of PTSD is influenced by a complex interaction of biological, cognitive and psychosocial factors". Any symptom clinically noted arises from an ecology, with a dozen interrelated systems that have feedback and feedforward processes (Foa et al., 2009). A systems approach to treating PTSD would require training professionals to be aware of these systems and explore which treatment or approach might provide greatest leverage for positive change.

There are some adopters of a more systemic response. The practice guidelines from the International Society for Traumatic Stress Studies (Foa, et al., 2009) call for concurrent treatment of comorbid issues and an integrated approach. Integration of a mind-body based approach and the interplay of body, mind and chemical systems is a growing theme in the literature and research. Among them, the polyvagal affect, the hypothalamic-pituitary-adrenal axis, and neurobiology have been useful (van der Kolk et al., 1996).

Pharmacological treatment

Pharmacological treatment for PTSD symptoms is commonly used, often with ongoing reliance. This began before WWI, where tranquilizers and painkillers were employed (Friedman, 2018). Since then anti-depressants, antipsychotics, hallucinogenic methamphe-tamines and β-adrenergic receptor antagonists have also been tried. These exhibit moderate *strength of evidence* (SOE) with the *number needed to treat* (NNT) at 2, meaning they were very effective but the impact size was small to medium as measured by point reduction in Clinician-Administered PTSD Scale (CAPS) when compared with placebo (Jonas et al., 2013).

Overall effectiveness of pharmacotherapy is lower than cognitive and non-trauma focused treatments (Lee et al., 2016). The main problem with pharmacotherapy is that the effects do not last after the veteran ceases taking them, and they only provide symptom suppression. In addition, they have relatively low *numbers need to harm* (NNH), meaning it is very easy to harm the treated. The use of psychopharmacologic drugs (such as chlorpromazine) has an NNH of 2 (Adams

et al., 2012). The use of pharmacological intervention has an overall NNH of 3 (Aetna, 2015).

There are also issues with polypharmacy, with 75% of military personnel in one meta-analysis diagnosed with PTSD having a co-occurring substance abuse disorder, with self-reported abuse of both psychoactive recreational drugs and pharmaceuticals (Searcy et al., 2012).

Psychological treatments

The history of psychological treatment for PTSD began with French neurologist Jean-Martin Charcot, who treated hysteria, paralysis, contractures, arc-de-cercal and neurosis. Sigmund Freud and Josef Breuer treated their patients as though they were having an unconscious reaction (symptom formation) to trauma. Each treated PTSD with non-conscious and non-rational approaches: Charcot with hypnotism, Freud with unstructured narrative development and dream therapy, Breuer with catharsis (Andreason, 2010).

Since then there has been a shift to more conscious, rational, cognitive approaches, for example Cognitive Behavioral Therapy (CBT) (Friedman, 2018). PTSD treatment guidelines have consistently advised cognitive therapies including Cognitive Processing Therapy (CPT), Cognitive Therapy (CT), Cognitive Behavioral Therapy (CBT), Trauma Focused CBT (TF-CBT), Cognitive Restructuring (CR), Interpersonal Therapy (IT), Psychodynamic Therapy and Narrative Exposure Therapy (NET) as first-line treatments (ACPMH, 2013; Cusack et al., 2016).

From a sufferer's perspective, PTSD is a response to trauma and is deeply unconscious, non-rational, highly ordered and idiosyncratic (van der Kolk, 2014). CBT and similar therapeutic approaches aim to work rationally (consciously) to amend or alter non-rational responses. Interventions like Eye Movement Desensitization and Reprocessing (EMDR), Virtual Reality (VR), Hypnosis, Mindfulness Meditation, Reconsolidation of Traumatic Memories (RTM), Neurofeedback, Biofeedback, Mindfulness Based Stress Reduction (MBSR), Present Centered Therapy (PCT) and Trauma informed Coaching (TiC) tend to operate more directly with the unconscious.

Cognitive, rational approaches require question/ answer skill, introspection, being present to self and being present to now, and/ or involve re-activating/ reliving to past memories of trauma, or the construction of a narrative for the trauma. NET, the most successful of them, is not necessarily a conscious, cognitive process, calling on the shattered fragments of memory. It is partly an emotional, unconscious process, but nevertheless we have included it here, because it is at the consciously aware end of the spectrum (Neuner, 2004).

Cognitive treatments have a quite low rate of success. Although one large meta-study found that 49-70% of veterans receiving CPT and Prolonged Exposure Therapy (PET), now the most frequent treatment, attained meaningful reduction of symptoms; 66% of them were still diagnosed with PTSD after treatment (Steenkamp et al., 2015). Watts et al. (2013) note that soldiers and veterans diagnosed with PTSD benefit less from psychotherapy than non-military populations. Perhaps more tellingly however, 78% of veterans are still in treatment after 4 years (Congress of the United States, 2012, as referenced in Haagen, 2015).

CBT, the most widely deployed first-line therapy, has a moderate strength of evidence (SOE) for loss of diagnosis of PTSD (Cusack et al., 2016), which Bryant (2015) states as 33% of Veterans entering treatment becoming symptom free. A further 33% experience short term or partial improvement, with about half of those going into recidivism. The final 34% are refractory (being non-responsive). Kar (2011) puts the non-response rate to treatment at 50% and says comorbidity and the exact nature of the group going through therapy are possible reasons for the high rate of failure.

In some cases, the approach of utilizing prolonged exposure, imaginal exposure, fragmented narrative exposure and exposure therapy CBT retraumatize patients, including attempted suicide, successful suicide, hospital admission for suicidal ideation or self-harm (Neuner, 2010; Schnurr, 2003). There is large response variability from one study to the next: NNT was a moderately effective value of 6 (on average it takes six people treated for one to be helped), but just over 10% of those treated (1 in ten) experience an exacerbation or increase in their symptoms (Foa et al., 2002) and often the treatment causes them harm (Lilienfeld, 2007). However, there is evidence from meta-analysis that this figure may be low due to under reporting of adverse effects (Cusack et al., 2016).

Tables 2 and 3 below contrast treatments which are dominantly rational and those which are predominantly non-rational in their approach. Some treatments may overlap categories, and some treatments may only be used on connection with others (such as bio-feedback or art therapy). Note that the most recent review of effective treatments (Forbes et al., 2019) place EMDR among the cognitive approaches. We place EMDR among the non-cognitive therapeutic alternatives as it relies upon adaptive information

processing (AIP) and sensory reprocessing instead of cognitive (thinking) talking therapy focused on the trauma (Frappell-Cooke, 2019).

TABLE 2: The Effectiveness of Cognitive Treatment Alternatives for PTSD in Veterans (small number trials, mixed result and non-veteran studies excluded)

Treatment	Efficacy (% response and how much response)	Known side effects
Cognitive Behavioral Therapy (CBT/ ET/ PE)	33% treated have no symptoms after therapy, 33% have some symptoms, 33% are refractory (Bryant, 2015). Using Bradley et al. (2005) 0% symptomatic change or improvement for ET (Glynn et al., 1999); 0% diagnostic change, 63% improvement for ET (Keane et al., 1989); 0% diagnostic change, 45% improvement for trauma focused group therapy (Schnurr et al., 2003).	10.5% experience an exacerbation or increase in their symptoms (Foa et al., 2002). CBT has NNB = 6 (Paykel, 1999; Jonas, 2013).
CPT	CPT 49-70% of veterans receiving Cognitive Processing Therapy and prolonged Exposure Therapy (ET) attained meaningful improvement in their symptoms, but 66% of the same retained the PTSD diagnosis after treatment (Steenkamp et al., 2015).	CPT has NNH = 10 (Andrews, 2014, when using an internet-based intervention). NNB = 4 (Jonas, 2013)
Narrative Exposure Therapy (NET)	71% non-symptomatic after therapy (Neuner, 2004).	Not reported

TABLE 3: Effectiveness of Non-conscious Treatment Alternatives for PTSD in Veterans (small number, trials, mixed result and non-veteran studies excluded)

Treatment	Efficacy	Known side effects
Eye Movement Desensitization Reprocessing (EMDR)	Reduces between 50 and 100% of the symptoms list for PTSD (Chemtob et al., 2000; Rothbaum et al., 2005; van der Kolk et al., 2007).	Withdrawal from adverse side effect (Hogberg et al., 2007)
Reconsolidation of Traumatic Memories (RTM)	96% of the participants are symptom free, PCL-M score halved (Gray & Bourke, 2015).	Not reported
Imaginal Exposure (EI) & Imagery Rescripting (IR)	63% improvement in symptoms (Arntz et al., 2007).	Not reported
Virtual Reality (VR) flooding	90% reduction in symptoms (Difede & Hoffman, 2002).	Not reported
Trauma Coaching (TC)	Significant improvement on anxiety, depression and stress (Wake & Leighton, 2014; Gyllensteen & Palmer, 2005).	Not reported
Yoga & Meditation	Improves depression, reduce intrusive thoughts, and reduce hyper-arousal (Brown & Gerbarg, 2005).	Not reported
Art Therapy (AT), Mindfulness Based AT and Art Therapy Trauma Protocol (ATTP)	Effective in treating a variety of symptoms (Slayton et al., 2010), including improving participation and reducing avoidance (Skeffington & Browne, 2014).	Not reported
Brainwave Therapy & Neurofeedback	Highly effective for symptom reduction (Peniston & Kulkosky, 1995).	Not reported

Body Oriented Therapy	Excellent improvements in physical, mental and sexual problems (Röhricht, 2009).	NNH > 18,000 (Ventegodt & Merrick, 2009).

Several studies have done a direct compare and contrast between the two modalities, in one case CBT vs. EMDR. A systematic meta-analysis of the effectiveness of CBT in 23 clinical trials treating PTSD found that CBT resulted in better remission rates than EMDR (Mendes et al., 2008). Another meta-analysis, of EMDR effectiveness, indicated strong support that eye movement contributed strongly to processing emotional memories (Lee & Cuijpers, 2013). EMDR is now recommended as first-line treatment (Korn, 2009) along with Exposure Therapy and prolonged exposure as the 'gold standard' (Rauch et al., 2012). However, research on the effectiveness of EMDR for military populations with PTSD is ongoing, with a meta-analysis of RCT's concluding it is "effective", but recommends more research be done because of a disparity in measurements of effectiveness (Frappell-Cooke, 2019).

One large study showed that when offered the voluntary choice of treatment or therapy in the face of trauma, an overwhelming proportion of the population move away from CBT and cognitive therapy toward non-conscious alternatives like EMDR (Marshall & Suh, 2003).

From silos and divisions to holistic and wellness

Areas of expertise and research operate in silos, characterized by poor information sharing, and they lack a holistic approach. D'Andrea et al. (2011) observed that, "Most research on mechanisms [of PTSD] occurs within a 'silo' of research expertise: neuroanatomists, endocrinologists and immunologists work independent of one another." Silos are not a true reflection of PTSD. The condition is a disruption to an individual's ecology: neurological, pathological, psychological, biological, social, structural, emotional and neurochemical.

The D'Andrea et al. study goes on to say, "Given that a link between trauma and multiple physical illnesses is well-established, collaboration across subspecialties may enhance clarity in the field". A movement away from a siloed, linear approach toward an integrated, holistic study of all that is going on for the patient will enhance everyone's outcomes.

In their forecast, Olff and co-workers (2015) advocated an integrative understanding and treatment of PTSD across modalities and the use of multidimensional models: phenomenological, neurobiological, physiological and psychological.

Elements of personal ecosystems

The human ecosystem has neurological, genetic, epigenetic, endocrine, hematological and neurochemical, microbial, gut-biome and physical sub-systems that change in response to a potentially traumatic event (van der Kolk, 2005). The literature for these various systems provides a diverse array of mechanisms present for the treatment of PTSD.

Neurology

Neurology, including the central and autonomic nervous systems, is central to the individual's response to stress and trauma. The initial reaction to a potentially traumatic event invokes diverse coping mechanisms. Freeze, flight and fight are well-documented responses, involving the brain stem and elements of the para-limbic structures. In PTSD these responses continue beyond the event, and with repeated activation can lead to reduced cortical density in specific areas of the brain. In turn, this can reduce or enhance fear acquisition and extinction capabilities and affect executive functions (Herringa et al., 2012). Experiences include hypervigilance, anger, physical numbing, reduced interoception and blunted proprioception (van der Kolk, 2014). Reliance on alcohol and drug use to cope are commonly reported (likely underreported), and many avoid social interaction by physically withdrawing, growing silent and amending patterns of behavior to keep them hidden from attention (van der Kolk, 2014).

PTSD is a condition of unwanted re-experience of past events concurrent with the inability to be present. There is also a tendency to be hypervigilant about the future, which is expressed as anxiety (van der Kolk, 2009).

Memories of past events are often shattered and fragmentary, with no narrative. The ability to encode new memories, and recall verbal memory may also be impaired (Johnsen & Asbjørnsen, 2008), as does the functional knowledge they have about self. We know that knowledge of self is normally remembered and recalled better than semantic or event-related memory (Craik et al., 1999).

The PTSD brain appears to be changed in the way it activates thinking about the relevance of information for self, others and comparative judgements. This seems to be correlated with changes in the amygdala, hippocampus and hypothalamic-pituitary-adrenal axis (Kelley, 2002). More specifically, after trauma, there is reduced cortical volume and grey matter density in the hippocampus, amygdala (Morey et al., 2012), prefrontal cortex, ventral prefrontal cortex, locus coeruleus, anterior cingulate, insula, orbitofrontal

cortex, subgenual cingulate, caudate nucleus, hypothalamus, middle temporal gyrus and right medial frontal gyrus (Herringa et al., 2012), pregenual anterior cingulate cortex and subcallosal cortex (Rauch et al., 2003). Some of these changes happen rapidly, over weeks and some take longer, over months.

It is surprising, given the ubiquitous loss of neuronal material (and overall brain size), that more research has not been done on how it can be re-established. Research on neural connections and density would seem to indicate regrowth occurs as a result of the treatment, yet there are only three studies that have examined cortical volume:

- CBT has, in one study, increased cortical volume (Levy-Gigi et al., 2013).
- Anti-depressants have, in one study, increased cortical volume (Vermetten & Bremner, 2002).
- Lithium has, in one study, increased cortical volume (Yucel et al., 2008).

In addition to these, ECT has, in one study, been shown to increase cellular proliferation (Nordanskog et al., 2010). TF-CBT and EMDR have been shown to assist in re-adaption of functional connectivity affecting bilateral temporal pole connection (Santarnecchi et al., 2018).

Genetics & epigenetic change

The study of polygenetic influences in PTSD as a precursor to, indicator for, or as an epigenetic change resulting from trauma, is relatively new. There are three ideas running through the research: (i) some genes may predispose soldiers to risk factors in a battle situation; (ii) some genes could make a veteran more susceptible to re-exposure (in life, therapy or continuing in a military environment); (iii) through epigenetic processes and their own response to those risk factors, the soldiers may initiate a permanent neurochemical and neuroplastic change.

So far seven major genotypes have been identified for study because of their involvement in the neurochemistry and/ or systems involved with PTSD (Broekman et al., 2007). These are:

- Gastrin Releasing Peptide (GRP, STMN1) and serotonin (5-HTT esp. SLC6A4);
- Brain-derived neurotrophic factor (BDNF);
- Glucocorticoid receptors (FKBP5 mRNA);
- Dopamine (DRD2, DAT1);
- GABA (GABRB & GABRB3) and benzodiazepines (Vaiva et al., 2006);
- Apolipoprotein systems (APOE2, ApoE-ε2);
- Neuropeptide Y (NPY).

A longer list of genes implicated in the search for predisposition to PTSD have been provided by Blum et al. (2012) who, in addition to the above, added: Opioid-R mu-1 (OPRM-1); high GILZ mRNA; DBH; NF-κB; Monoamine B; CNR1; Myo6; CRF-1 & CRF-2 receptors; and GR genotypes N363S & Bc1l GG.

The only studies that have looked at the epigenetic changes associated with psychological treatment examined the way that CBT alters the expression of some genes, especially FKBP5 (Levi-Gigi et al., 2013), through altering glucocorticoid reception, metabolism and immune response and reducing cortisol effectiveness in the brain (Mahon et al., 2013).

Neurochemistry: endocrine, hematological and neurochemical

In responding to potentially traumatic events, some neurochemicals act in concert, in combination and across several axes in the body (Kendall-Tackett, 2009). These responses often begin immediately and are temporally variable. Initial research focused on norepinephrine and cortisol, adrenocorticotrophic hormone, epinephrine and corticotrophin-release factor (Schore, 2009).

Research in this area has been pursued in five directions:

- Cortisol and Norepinephrine (separately and together);
- Adrenocortical activity;
- Serotonin;
- T-cells, cytokines, interleukins and plasma; and
- NDMA & D-cycloserine.

The results of this research could be very useful when designing ways to test the effectiveness of therapy. For example, urine tests of those suffering PTSD have shown low levels of cortisol with elevated levels of norepinephrine when compared to other hospitalized groups (Mason et al., 1988). The N/C ratio is twice as high, with a mean ratio of 2.54 compared to a mean of .99 in the control. The ratio of cortisol to norepinephrine (N/C) could potentially be used as a marker for improvement in the condition and a return to wellness.

The balance of the neurochemicals serotonin, cortisol and norepinephrine mediate the sensation of dullness, numbness and lethargy. Sleep is commonly deeply disturbed with nightmares relating to the content of their experience.

Those suffering PTSD have higher lymphocyte activation markers. Although the increase is just 4%, it indicates a chronic immune system response similar to

that seen in people with autoimmune disease (van der Kolk, 2014). Further research is required to explore the significance of this for PTSD patients because neurochemical treatment for lymphocyte reaction in PTSD (immunosuppressive therapy) is still in its infancy.

Neurochemical treatments include:

- Cosyntropin, which promotes higher cortisol levels. Treatments that assist in raising blood cortisol and lowering norepinephrine may be used to lower PTSD symptomatology (Golier et al., 2014);
- Administering hydrocortisone after exposure to trauma prevents PTSD response (De Quervain, 2008);
- Administration of propranolol (a β-adrenergic receptor antagonist) reduces PTSD symptoms (Pitman et al., 2002);
- Pressure based therapies (which are perioperative, goal-directed, hemodynamic therapies based on radial arterial pulse pressure variation and continuous cardiac index trending) release serotonin, reduce cortisol, decrease activity in the amygdala and hippocampus, and de-activate the paralimbic and neocortical systems (Bloch-Atefi & Smith, 2014);
- Chemical treatments using hydrocortisone to artificially simulate the circadian rhythm assisted in returning sleep and relieved nightmare symptoms; similarly, Prazosin has been effective in removing nightmares (Yehuda, 2006; Thompson et al., 2008).

As patients respond successfully to treatment, and become asymptomatic, it is possible that many bio-markers change back to 'normal' along with other changes in perception, thinking, behavior, choice and neurochemistry. Yet, the occurrence and extent of such changes is unclear and needs to be explored by further research.

Molecular Biology: metagenomics

The molecular biology of PTSD is concerned with biology, chemistry, epigenetics, pathophysiology and biochemistry at a molecular and cellular level. Through metagenomics, it is becoming increasingly apparent that the microbiome (mainly the bacterial aspect), and the direct relationship it has with the rest of the human organism is critically important for wellbeing. The microbiome also has an indirect influence on epigenetics through switching gene expression on or off, and the gut microbiome appears to play a pathophysiological role in brain disorders including autism, bi-polar disorder, anxiety, depression and PTSD (Naviaux, 2014).

The effects of PTSD are thus felt in multiple systems including: the gut-brain axis, the hypothalamic-pituitary-adrenal axis, hypothalamic-pituitary-thyroid axis, and the sympathetic-adrenal-medulla axis. This leads to reduction in homeostatic regulation (McEwen & Wingfield, 2003).

Studies are focusing on each phase of digestion, particularly the cephalic phase, where the brain is involved in the preparation of enzymes, and the intestinal phase, where nutrients and neuropeptides digested from food enter the bloodstream. These studies have revealed that "When our bodies are in post-traumatic stress, they respond to food as a threat. When we eat under stress, we interrupt all the phases of digestion." That is, we are hypervigilant and we bypass this phase almost entirely (David & Rosen, 2014). A growing body of pre-clinical literature further demonstrates the two-way link in both affect and signaling between the brain and the gut microbiome. For example, through altered biome behavior, increased peripheral blood mononuclear cell and T-cell profiles, with a decrease in microRNA miR-125, alters interferon gamma, which promotes inflammation (Zhou et al., 2014).

These findings perhaps explain the comorbidity of gastrointestinal disorders such as ulcers and IBS in soldiers and veterans who experience PTSD (Stam, 2007).

Conclusion and Applications

PTSD is not a disease in the same sense as Alzheimer's or Parkinson's disease. PTSD is a failure to recover after a potentially traumatic event. It is often a highly ordered response, although those with PTSD often suffer a disordered life. For optimal prevention and treatment in soldier and veteran populations, we recommend a holistic approach to this debilitating and costly condition. Specifically:

1. *Move away from diagnostic symptomatology.* Thomas Insel, Director of the NIMH (US), has moved funding away from research driven by symptomatology (Insel, 2010). DSM 5 has been criticized for taking an overly diagnostic approach, which produces both false positives and false negatives in recognizing PTSD. This brings unnecessary delay in treatment and pain to the veteran. Instead of "chasing after diagnostic categories", they call for a domain of research and therapeutic choice.

We wholeheartedly agree. The diagnostic system and the DSM-5 have been abandoned by the

NIMH. A holistic ecosystems-based approach should be considered in its stead.

2. Augment conscious and cognitive treatment with nonconscious methods. Treatment of PTSD began with the use of a nonconscious method, targeting or cooperating with the unconscious, which have learnt to respond to the environment in certain ways. As Tables 2 & 3 show, therapies based on nonconscious method are, in the main, more effective than highly rational methods, especially when considering the measures of 'do **no** harm'. This makes obvious sense as there is minimal risk of re-traumatizing during treatment if there is no attempt at conscious re-exposure.

Researchers are suggesting a wide range of nonconscious methods to improve treatment efficacy, as alternatives or adjuncts to CBT, ET and CPT. For example, those already receiving therapy may be sent for polysomnography to understand the interaction between sleep, PTSD and the unconscious to address PTSD (Shalev et al., 2000).

3. Move away from silos toward integrated approaches. Scientists undertaking research on PTSD have approached it from their individual and respective areas or silos of discipline. Psychology and psychiatry; neurology and neuroscience; genetics and epigenetics; neurobiology with its focus on endocrine and pathological systems; and molecular biology with metagenomics and studies of the microbiome have all contributed to our understanding. At present, few of the studies available are examining those systems together, or the impact of treatment upon them all.

The highly inter-related nature of these systems and the sequelae of events proceeding become important because of the feedback, feedforward and amplification effects. Treatment regimes should consider the entire human ecosystem.

The Gallipoli Research Foundation, who conducted the largest longitudinal study of Vietnam veterans in Australia, sees the future of their study as developing and trialing novel prevention strategies such as identifying biomarkers for screening at-risk individuals (Dwyer, 2015). This screening must identify pre-event psychosocial and neurobiological risk and resilience factors if very early efforts at prevention and early intervention are to work (Safir et al., 2015). D'Andrea et al. (2011) observe, "Given that a link between trauma and multiple physical illnesses is well-established, collaboration across subspecialties may enhance clarity in the field".

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