STATEMENT BY

THE HONORABLE JONATHAN WOODSON, M.D.

ASSISTANT SECRETARY OF DEFENSE (HEALTH AFFAIRS)

REGARDING

MENTAL HEALTH RESEARCH

BEFORE THE

HOUSE ARMED SERVICES COMMITTEE
PERSONNEL SUBCOMMITTEE

APRIL 10, 2013

Mr. Chairman, Members of the Committee, thank you for the opportunity to appear before you today and discuss mental health research and, I'll also address research related to traumatic brain injury and suicide prevention, which often have some co-occurring mental health aspects.

Since September 11, 2001, more than 2.1 million Service members have deployed to Iraq and Afghanistan in OPERATION IRAQI FREEDOM, OPERATION ENDURING FREEDOM, AND OPERATION NEW DAWN. Military forces sent to fight those wars have exhibited a number of unique features, including: (1) an all-volunteer military that has experienced multiple deployments to the war zone, (2) substantial use of the Reserve Components including the National Guard, and (3) a high number of Service members surviving severe injuries that in previous wars would have resulted in death. These sustained combat operations resulted in greater exposures to stressors, including exposure to death, risk to life, threat of injury or actual injury, not to mention the day-to-day family stress inherent in all phases of the military life cycle and its transitions. Stress can be a major contributor to the onset and exacerbation of mental health problems and is related to a variety of negative physical health outcomes.

Some Service members have experienced traumatic brain injury (TBI); symptoms of mental illness, including depression and posttraumatic stress disorder (PTSD); and suicidal thoughts or behaviors. Complicating the prevention and treatment of mental health disorders, TBI, and suicidal behaviors, are chronic pain, insomnia, substance abuse related to alcohol, tobacco, and other drugs, as well as the misuse and abuse of prescription drugs. Family members often suffer with the Service member because of the multiple stressors associated with deployment and reintegration. Overall, we expect the need for mental health services for Service members and their family members to increase in coming years as the Nation recovers from the effects of more than a decade of military conflict.

Research efforts to address these health care needs are many and on-going. Military Health System (MHS) researchers are attempting to answer questions across the research continuum from diagnosis through treatment to follow-up care. However, fundamental gaps in scientific knowledge remain, so we continue to pursue the research described herein.

Critical to the development of DoD research planning is an understanding of the agency-specific activities in the Department of Veterans Affairs (VA), the Department of Health and Human Services (HHS), and the Department of Education (ED). The DoD works closely with the VA, HHS, and ED to best leverage inter-agency research investments to advance health care and health services. This was most recently achieved in a Joint Review and Analysis meeting on research related to PTSD, TBI, suicide prevention, and substance abuse.

Agency representation at the meeting included DoD, VA, ED (represented by the National Institute on Disability and Rehabilitation Research [NIDRR]), and HHS (represented by the National Institute of Health's [NIH's] National Institute of Neurological Disorders and Stroke [NINDS], National Institute of Mental Health [NIMH], and National Institute on Drug Abuse [NIDA]). Activities are underway in support of inter-agency collaboration, including the DoD's Systems Biology Program and the Millennium Cohort and Family Cohort Studies, the VA's Million Veteran Program , the NIH's biomarker research program, and research dedicated to advancing prevention and treatment interventions. The DoD and the Centers for Disease Control and Prevention (CDC) are partnering with the Brain Trauma Foundation to develop a clinically useful definition of mTBI/concussion. Suicide prevention research includes the DoD's Military Suicide Research Consortium (MSRC) and the NIMH and DoD Army Study to Assess Risk and Resilience in Service members (Army STARRS) program.

Data-sharing efforts include the DoD/NIH Federal TBI Research Informatics System (FITBIR) for TBI clinical research (a central repository for new TBI-related data that links to existing databases to facilitate sharing of information), the VA computing infrastructure, and NIDRR's TBI Model Systems National Database (TBIMS-NDB), which contains retrospective data on the clinical progress and outcomes of individuals with moderate to severe TBI. Research may benefit in multiple ways from the use of electronic health record data by providing information related to the feasibility of attaining study participants or understanding the scope of a problem being investigated.

Recently initiated activities include two new joint DoD/VA research consortia to support PTSD and TBI biomarker studies (the Consortium to Alleviate PTSD (CAP) and the Chronic Effects of Neurotrauma Consortium (CENC)), new treatment studies to be generated from biomarker studies, and new treatment response studies to be incorporated into clinical trials.

Key DoD research priorities span the mental health domain, including the need to:

- Identify new therapies and strengthen the evidence base for prevention and treatment interventions to improve health and function throughout the illness trajectory.
- Enhance post -mortem tissue collection and coordination of repositories to enable broad access to high quality post-mortem specimens, where permissible.
- Utilize common project tracking and research management systems to enhance communication, coordination, and collaboration across research funding agencies.
- Discover and determine viability of biomarkers to detect acute and chronic pathology, predict outcomes, and monitor the response to treatment.

- Accelerate the pace of research and development for PTSD, TBI, and suicide prevention by leveraging existing and emerging technologies to the greatest extent possible.
- Develop new outcome measures that are sensitive enough to evaluate changes across time

The sections that follow provide examples of the DoD research activities and research planning approach in mental health.

**PTSD: Mechanisms, Biomarkers and Treatment Research**

In response to a traumatic event, people commonly experience PTSD-like symptoms, e.g., hyperarousal or reliving the event. Many individuals progressively improve and symptoms recede. Those who continue to experience distress may develop PTSD. The overall goals of PTSD research studies are to (1) reduce the number of individuals who develop PTSD following trauma (through early diagnosis and preventive interventions) and (2) reduce the number of individuals with chronic PTSD (through treatments that also address substance-related and other comorbidities).

*Mechanisms.* The underlying mechanisms of progression following traumatic exposure need to be able to identify individuals at risk for developing PTSD and comorbid conditions. This may be attained through neuroimaging, animal studies, post-mortem analyses, and laboratory-based investigations focused on identifying physiological and neurochemical contributions, and other psychological, contextual, and environmental factors. As cognitive science evolves to reveal how dysfunction in memory and attention processes contributes to the development of mental illness, researchers need to translate these findings into prediction models and novel prevention and treatment interventions.

*Biomarkers for early diagnosis.* Research is needed to identify and validate biomarkers (biological markers) to predict increased vulnerability to the development of PTSD, to indicate changes in the spectrum of symptoms associated with worsening function, and to demonstrate at the biologic level a positive response to intervention. A biomarker is an objectively measured indicator that ideally is capable of reflecting normal, at-risk, and disease states as well as response to a therapeutic intervention. Combining different measures across biological, environmental, and social influences – the development of a "biosignature" – can help scientists understand the origins of disorders such as PTSD. Similar to the way physicians diagnose heart disease in patients by coupling blood test panels for cholesterol and triglyceride levels with measures of hypertension and high blood pressure, scientists may develop a biosignature for PTSD by combining cognitive measures and imaging data, serum and

cerebrospinal fluid markers, and highly relevant physiological markers for related symptoms.

A DoD research priority to enable identifying biomarkers is a systems biology approach, which involves the study and characterization of the perturbations that occur in biological molecules and pathways during the course of disease. Researchers funded through the DoD Systems Biology Initiative have identified a surprising number of potential biomarkers that may signal the presence of PTSD in humans. Beyond genomic investigations, another promising area is cognitive functioning. Basic cognitive tests of attention, memory, and executive functioning may be among the most promising predictors. Ongoing research is focused upon refining the numerous potential biomarkers down to a selected few that could be used to validate a gauge or measure response to intervention and a slowing or reversal of the disease trajectory.

A major new effort is the DoD's and VA's CAP. The CAP will allow investigators to jointly pursue research related to establishing surrogate and clinically actionable biomarkers for early PTSD diagnosis and treatment effectiveness. The CAP will seek to discover and validate PTSD biomarkers. CAP research activities will be informed by the newest scientific findings from investigations that are well under way.

*Biomarkers for treatment effectiveness.* The identification and validation of biomarkers for PTSD will ultimately enable the effectiveness of prevention and treatment interventions to be measured. Clinicians would be able to match individuals with the most effective prevention and treatment protocols, which may include medications, psychotherapy, and integrative and complementary medicine treatments alone or in combination. Research may reveal populations at risk for comorbidities, subsequently enabling the development and testing of interventions to prevent these problems as well as effectively treat these conditions if they occur. Thus, another important goal of the DoD is to facilitate the development of more personalized treatments, that is, individually tailored interventions with measurable responses.

*Treatments.* Psychotherapies and pharmacological medications are widely used to treat PTSD. When evidence-based psychotherapy treatment for PTSD is provided, up to 60% of patients will respond successfully. However, individual differences play an important role in the selection of the appropriate intervention. Individuals who do not respond to one treatment may be reluctant to try alternative treatments, and preferences relative to the types of therapies available (e.g., pharmacotherapy, psychosocial therapy, and complementary and alternative medicine) may have a significant impact on overall outcome. The use of combined therapies holds promise to address urgent mental health needs. In addition, individuals with PTSD

may present with substance abuse because alcohol or controlled substances may at least temporarily alleviate symptoms. Therefore, treatment research conducted will examine ways to optimally treat comorbid conditions (e.g., integrative versus sequential treatments). TBI will be examined as a comorbid condition. Thus, another DoD goal will be to improve and optimize current psychotherapeutic treatment regimens by using adjunctive techniques to enhance effectiveness and shorten treatment time to provide more rapid relief. There are no medications developed specifically for the treatment of PTSD. The two medications approved for PTSD (the antidepressants sertraline and paroxetine) show, at best, modest efficacy. Many medications are used off label to treat PTSD symptoms and lack the scientific evidence that they are beneficial. Few treatment interventions target underlying biologic causes or mechanisms of the disease. Investment by the pharmaceutical industry in new medications for PTSD has declined in recent years. The DoD will pursue the development of therapeutics targeting biomarkers and mechanisms uncovered in the course of research as well as assess the utility of repurposed or "off-label" treatments. A well-studied example of this would be prazosin's ability to treat sleep disturbances in PTSD (prazosin is approved for treating hypertension). In addition, new partnerships (e.g., public-private collaborations) will be pursued to aid in the identification of biologically plausible pharmacological targets for the prevention and treatment of PTSD.

**DoD Vision for Moving PTSD Treatment Research into Practice**

The overall DoD research goals are to prevent PTSD or effectively treat the disorder. Individuals exposed to traumatic events would routinely participate in systematic evaluation on broad dimensions of risk with progressively intensive diagnostic evaluations. Results would be weighted/combined in an automated algorithm to determine risk for PTSD and associated comorbidities (especially substance related) and to inform care and follow-up. Evaluations would inform interventions targeted at mitigating negative psychological symptoms and consequences. Individuals seeking care for PTSD would undergo a thorough medical, psychiatric, and substance abuse history and assessment to yield a health risk profile ("biosignature") indicative of the underlying cause/type of impairment. The individual would then be matched to receive treatment known to target/address the specific underlying cause/type of his/her disorder. Throughout a course of treatment, effectiveness of any administered treatment(s) would be measured. Researchers would have knowledge of both fixed and modifiable systems, circuits, and molecules to focus treatment development and refinement studies. Any individual would thus receive treatment matched to his/her unique symptom profile, and clinicians would better monitor individuals' responses to treatments. Individualized and staged interventions would be planned to minimize severity of acute stress and prevent the development of PTSD. New interventions thus will move faster from discovery/development to use in clinical care based on the next years of scientific discovery articulated in this vision.

**TBI: Biomarkers, Diagnosis, Mechanisms, and Treatment Research**
TBI is a complex and heterogeneous injury. It can result in temporary symptoms or enduring disabilities, depending on the severity and location of the injury, the age at injury, and the number of injuries over time. Common disabilities resulting from TBI include difficulties with cognition, behavioral and mental health, communication, and sensory processing. Physical symptoms such as headaches and sleep disturbances are also observed following mTBI. Moderate and severe TBI also have been linked with long-term consequences such as increased risk for Alzheimer's-type dementia, symptoms of Parkinson's disease, and the decreased ability to maintain social relationships. Factors contributing to slow progress in TBI research and thus limiting advances in clinical care include imprecise diagnostic tools and criteria used to classify the severity and type of TBI; a poor understanding of the impact of co-occurring conditions; gaps in understanding of mechanisms underlying injury and recovery; uncertainty about the ability of preclinical models to reproduce the spectrum of injuries and co-occurring conditions; and a nascent understanding of ways to harness neuroplasticity to increase repair and recovery. Notably, a context that poses a unique challenge is the role of multiple mechanisms ("blast-plus") as compared to single mechanism injuries (motor vehicle accident and athletic concussions).

*Diagnostic tools and definitions.* Current definitions of TBI as well as the tools currently used to diagnose it are imprecise. The DoD and the CDC, in partnership with the Brain Trauma Foundation, have funded an effort to develop a clinically useful definition of mTBI/concussion. Current definitions lack strong evidence to support their clinical utility to detect injury and predict outcomes. There is a need for leveraging newer and emerging imaging modalities such as diffusion tensor imaging and exploring the role of functional imaging in TBI research.

*Biomarkers for identification, management, and treatment effectiveness.* Preliminary evidence supports the potential for use of serum (protein) biomarkers to detect mTBI/concussion. Animal studies have indicated that changes in protein expression in white blood cells may identify inflammation related to TBI. However, identification of sensitive and specific biomarkers requires a more precise classification system for TBI, similar to the systems used for spinal cord injury and cancer. Biomarkers may inform research and clinical investigation as well as the management of both acute and chronic stages of TBI. Of particular interest are biomarkers indicative of the potential neurodegenerative effects of TBI, such as chronic traumatic encephalopathy and dementia. In short, biomarkers to detect injury, predict short- and long-term outcomes, and monitor response to treatment are all needed. Research studies are currently under way to identify and test biomarkers, but none are currently ready for clinical use.

*Mechanisms.* Following mTBI, most patients show some degree of functional improvement over time. However, relatively little is known about the mechanisms that underlie recovery or about ways to harness neuroplasticity to optimize improvements. Research is needed to identify patterns of brain structure and function that are associated with either recovery or poor response to treatment. Given emerging evidence regarding the chronic effects of TBI, a better understanding of the relationship between neurotrauma and neurodegeneration is needed to develop effective medical and rehabilitation interventions. The nature of brain injuries incurred in the current military conflicts has highlighted the need to better understand the effects of repetitive brain trauma on neuropathology, neurological function, and mental health.

*Preclinical modeling.* While basic science is essential to improve diagnostics and treatments for TBI, the ability to model TBI in animals has been less successful. None of the treatments found to be effective in preclinical animal models has successfully progressed through a Phase 3 clinical trial for clinical use in humans. The paucity of human post-mortem brain tissue available for study has not allowed sufficient comparison with that of animals. The differences in mass, shape, and white/gray matter ratios between rodent and human brains make it difficult to reproduce the effects of TBI in a manner that physically and structurally scales from rodents to humans. Animal models rarely address the short- and long-term comorbidities and/or chronic effects associated with TBI nor do they clearly address the recovery/rehabilitation phase. Systems biology approaches that integrate animal and human findings with computational modeling of injury mechanisms and high performance computing have the potential to enable previously impossible levels of cross-correlation and analysis of research data. A coordinated military, veteran, and civilian brain donor registry and tissue banking system to make post-mortem tissue available for research purposes is critical for guiding the development and validation of animal models, especially for mTBI.

*Treatments.* More than 30 clinical trials of TBI pharmacological therapies have failed to produce a U.S. Food and Drug Administration-approved treatment for TBI. There is limited evidence of the effectiveness of nonpharmacological interventions, including rehabilitation treatments, due in part, to underpowered studies and the paucity of validated assessment tools that are sensitive enough to detect treatment effects. Therapies may need to be customized to an individual's injury, predisposing factors, and co-occurring conditions and involve a combination of pharmacological and nonpharmacological interventions.

*Co-occurring conditions.* Major challenges to mechanistic and treatment-related research on TBI include difficulties in separating the effects of PTSD and other comorbidities, such as sensory, endocrine, cognitive, behavioral, and sleep dysfunctions and substance abuse, from the CNS injury itself. In other words, the

symptoms and sequelae of TBI can overlap with many other disorders. The common approach to intervention—independently treating symptoms associated with each diagnosis—is known to be less than optimal and is, in many cases, ineffective. Therefore, each domain in which there is a deficit requires a targeted, integrated approach for therapy. Additionally, research is needed to identify effective models of treatment for persons with TBI who also have co-occurring conditions.

**DoD Vision for Accelerating TBI Research to Improve Health Care and Outcomes**

The overall DoD goal for TBI research is to identify evidenced-based therapies that are effective in maximizing short- and long-term health and function and community participation and reintegration for persons with TBI. Effective treatments are needed to address the range of injury types and severities, the presence of co-occurring conditions, and the realities of access to care. To achieve this goal, it is necessary to make advances in several key areas related to diagnosing and characterizing the injury, measuring treatment effects, and understanding the mechanisms underlying injury and recovery, including the relationship between neurotrauma and neurodegeneration. Specifically, a clinically relevant classification system for TBI is required across the spectrum of injury severities, age, and chronic conditions, including milder single and repetitive injuries. Validation and standardization of existing and emerging tools and biomarkers for TBI and associated comorbidities are needed including: diagnostic biomarkers to identify those who have sustained a TBI; prognostic biomarkers to predict who will fully recover and who will develop sequelae, including dementia; and pharmacodynamic biomarkers to monitor the biologic response to therapy. More sensitive, reliable, and efficient tools ("gold standards") are essential for evaluating the effectiveness of treatments for TBI. These are needed for all outcome domains including physical, cognitive, and psychosocial functioning and quality of life. In parallel with the foundational research described earlier, achieving the vision for TBI research requires concurrent investigation of existing promising and new treatments, including rehabilitation interventions. Ultimately, successful translation of TBI research will result in improved quality of life for those with TBI and their families.

**DoD Suicide Prevention Research**

Suicide prevention is a top DoD research priority, and it benefits from cross-agency, collaborative efforts to maximize the ability to address the problem effectively. Suicide is the tenth leading cause of death in the United States, claiming twice as many lives per year as homicide. When not specified otherwise, suicide is defined herein as including completed suicides, suicide attempts, and suicide ideation. Suicide attempts are up to 30 times more common than suicide deaths and are more frequent among younger persons. Having made a suicide

attempt is one of the most highly predictive factors for later suicide death. Individual characteristics, such as a history of childhood abuse and mental and/or substance use disorders, can interact with current or ongoing stressors (e.g., relationship disruptions, financial or social losses, and shameful experiences) to increase suicide risk. The suicide rate has been rising in recent years, both in civilian and military communities. Because individuals become suicidal for many different reasons, and not all individuals in suicidal crises will be seen in health care settings, multiple intervention approaches in multiple contexts are needed. Analyses to date indicate that no single factor has emerged as predictive of suicide in the military population. Some factors (such as repeated deployment) thought to be contributing to the increase in suicides in recent years have not been found to drive this increase (e.g., many suicides precede deployment). Almost half of the accidental and undetermined deaths investigated in the Army during 2006–2009 involved drugs or alcohol, and three-quarters of these deaths involved prescription drugs; however, the exact role of substance use in these deaths is not understood. Some studies have shown an association between suicide and TBI. However, the low base rate of suicide makes disentangling this challenging. Pre-existing factors may be a stronger contributor to suicide risk compared to TBI, Overall, factors leading to suicide are extremely complex and research is under way to better understand what role concussions may play.

Many individuals who die by suicide are seen in health care systems close to time of death. Evidence demonstrates that providing continuity of care through transitions (within a health care system and from military to civilian settings) is important. Other health care system improvements that reduce suicide risk include providing 24-hour crisis services, addressing poor treatment adherence and managing patients with comorbid substance use disorders, and providing regular training to frontline clinical staff on the management of suicide risk.
Factors that may help reduce suicide have been identified. For example, limiting access to lethal means significantly lowers suicide risk (e.g., restricting access to prescription drugs, limiting access to guns, using gun locks). Furthermore, treatments such as psychotherapies focused on mitigating suicidal thoughts among suicide attempters have been shown to reduce attempts by half in the 12 months following treatment. Small proof-of-concept studies show promise for fast-acting medications (e.g., ketamine) in reducing suicide ideation, but more research is needed. Longer-term research is needed to better understand the factors that build resilience and offer protection from suicidal behaviors and promote wellness and recovery. The DoD and NIMH jointly initiated Army STARRS to examine how psychosocial, biological, and genetic factors convey risk/resilience for suicide, as well as related conditions (e.g., mental health disorders and substance-related disorders). The Military Suicide Research Consortium was created by the DoD to develop and validate effective interventions to prevent suicide among active duty service members and veterans. It is a multidisciplinary collaborative consortium

on suicide prevention research, including VA and academic researchers. The Defense Suicide Prevention Office's Translation and Implementation of Evaluation and Research Studies (TIERS), which involve the DoD, military services, VA, and NIMH, translates knowledge accrued from evaluation and research studies into practical guidelines for military leaders, chaplains, and clinical and nonclinical support personnel, which will benefit Service members, veterans, and their families. A joint VA-DoD database of suicide history and health care information is under development to serve programmatic evaluation needs.

**DoD Vision to Advance Suicide Prevention Research**

The overall DoD goal for suicide prevention research is to achieve a significant reduction in attempted and completed suicides in military populations. The hope is that with new knowledge gained from research applied to practice, an individual who has made a suicide attempt or has suicidal thoughts would receive life saving care. Such an individual would be identified early either in their community or through their health care systems that would provide evidence-informed evaluations to include suicide screening and monitoring of stressors that might elevate an individual's risk. Once identified, patients would be matched to the appropriate level of immediate effective care and follow-up including safety planning throughout all levels of the quality care system. Malleable risk factors (e.g., reduced substance use, improved problem solving) that are identified could be targeted and help to avert reattempts. Prevention programs would exist that build resilience, reduce risk, and prevent the emergence of suicidal behaviors, and these programs would be implemented in diverse systems of care and populations based on emerging evidence.

**Sharing PTSD, TBI, and Suicide Prevention Research Data**

Access to study-level data for the purpose of secondary data analysis is important for research in general. Sharing of data allows researchers to increase the amount of data that can be combined or compared. Many smaller sized studies are able to involve only a modest number of participants; therefore the ability to share data when appropriate will increase the power for analyses and potentially accelerate research progress. In addition, large scale studies provide a platform for rich secondary data analyses when data sharing is accomplished. The FITBIR Informatics System has been established to provide a data repository for TBI clinical research. FITBIR was funded by the DoD and subsequently developed and managed by the NIH. Clinical data are entered into FITBIR utilizing the TBI CDEs, which were developed to allow greater comparability of TBI research data. Additionally, the TBI CDE project is developing data standards to allow expansion of FITBIR to preclinical work, enabling advancement of preclinical knowledge and improved modeling of TBI. This data repository decreases costs to the researcher, standardizes the collection of research data, and allows access to

researchers outside the original research studies to re-analyze and compare data across studies.

**DoD Vision for Research Data Sharing**

Research data sharing, ideally, would be collaborative and promote team science to more rapidly and effectively fill gaps in knowledge that will ultimately improve health care and outcomes. Research scientists and clinicians across the MHS and federal agencies would be able to submit and access data in a participatory manner in order to test new hypotheses, combine data sets for meta-analysis, and compare and contrast findings across disorders, the lifespan, and the continuum of care. Research data and protocols would be standardized to the greatest extent possible, and also aligned with clinical data to enable greater integration of research and clinical practice.

**Conclusion**

Scientific progress is incremental and takes time, but Service members and their family members need more effective treatments immediately, so our research mission is urgent. Research studies will plan for integration of findings into health care systems to address the goal of improving access to mental health services. The MHS will strive to have the embedded capability of evaluating the programs they are implementing, to determine their effectiveness in a specific setting, and to identify areas in which additional research is needed. This will be the MHS platform to integrate and embed emerging evidence-based practices in a "learning health care system," one in which health care providers, systems, and patients participate in the generation of knowledge on trends in health and illness, the identification of best practices for screening, assessment, and intervention, and the assessment of the impact of practice changes.

I am both pleased and proud to be here with you today to represent the men and women of the Military Health System, and I look forward to answering your questions.