



## APPENDIX B

# Fiscal Year 2019 Research Narrative by Division

## Behavioral Science Division

*The Behavioral Science Division (BSD) in Boston, Massachusetts, conducts research on life adjustment after military deployment and other traumatic stressors, methods to assess trauma and posttraumatic stress disorder (PTSD), innovative approaches to clinical intervention and treatment delivery, and the potential neurobiological and genomic basis of PTSD and its comorbidities.*

### Biomarkers

The Division has an active portfolio of genetic and neuroimaging studies involving collaborations with investigators in the [Translational Research Center for Traumatic Brain Injury and Stress Disorders \(TRACTS\)](#), the [Department of Veterans Affairs \(VA\) National PTSD Brain Bank](#), the Psychiatric Genomics Consortium (PGC), and the PTSD Working Group of the ENIGMA (Enhancing Neuroimaging Genetics through Meta-Analysis) Consortium. During FY 2019, Division investigators focused on the roles of inflammation and oxidative stress in the biology of PTSD, and on the role of PTSD and other trauma-associated symptoms in accelerated aging.

Ongoing studies that examine PTSD and blast-related traumatic brain injury (TBI) in Veterans of Iraq and Afghanistan war zones aim to clarify the relative contribution of mild TBI and psychiatric conditions to deficits in current functioning

and health outcomes. Investigators are now expanding this work to an older longitudinal cohort to study how stress, genetic risk, and peripheral biomarkers of inflammation are associated with subsequent health decline and neurodegeneration.

Biomarkers examined by the Division include brain features measured by neuroimaging, peripheral markers of inflammation and metabolic pathology, and specific genes and polygenic risk scores. Also under investigation are epigenetic markers drawn from blood and postmortem brain tissue, including epigenome-wide DNA methylation levels and transcriptome-wide mRNA (i.e., gene expression).

Division researchers continued to use functional and structural magnetic resonance imaging (MRI) to identify neural circuitry involved in PTSD. They also used magnetic resonance spectroscopy to examine neurodegeneration and neuroinflammation.

### Treatment Efficiency, Effectiveness, and Engagement

The Division's pioneering research on treatments for PTSD is focused on overcoming barriers to seeking care, reducing dropout, and increasing the efficiency of care delivery. One example is the internet-based treatment [VetChange](#), which was originally designed for Iraq and Afghanistan combat Veterans who report both risky use of alcohol and PTSD-related distress. The initial clinical trial produced evidence that VetChange was effective in reducing both drinking and PTSD symptoms. VetChange was subsequently modified to include mobile-friendly features and was disseminated nationally; this later version, which is applicable to Veterans of all eras, has been shown to be effective as well.

[A VetChange mobile app](#) that has key VetChange features was developed recently, in conjunction with the Dissemination and Training Division, and efforts are currently underway to integrate the mobile app and web versions to increase mobile access for real-time intervention support. In addition, a major extension of the VetChange web intervention is underway to directly integrate with clinical care delivered by VA providers and to evaluate its effectiveness in VA PTSD clinics as well as inpatient detoxification

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settings.

Other Division efforts include developing and testing efficient, therapist-delivered interventions or treatment extenders, with the goals of finding approaches that require less professional staff time and that are easier for patients to complete. A prime example is Written Exposure Therapy (WET), a five-session exposure-based treatment for PTSD that has been shown to be highly effective with non-Veteran patients. A current VA-funded study is being conducted to examine the efficacy of WET in comparison to Prolonged Exposure (PE) with Veterans. An implementation study is also being conducted in which VA mental health providers are being trained to deliver WET.

Research on factors that link PTSD with aggression toward intimate partners has led to the development and evaluation of interventions that reduce or prevent aggression within at-risk military and Veteran families. Positive clinical trials have been published, and the interventions continue to be implemented across the VA health care system and on one military installation. An ongoing pilot study also is testing one of these programs in an underserved urban civilian setting. Data collection is nearing completion, with preliminary analyses showing large effects in reducing intimate partner violence (IPV).

Division investigators have also been studying how clinicians make decisions around family involvement in PTSD treatment, conducting qualitative interviews with staff and administrators to identify their decision-making process and various barriers or facilitators for

family involvement. Efforts are also underway to examine how to harness social support from Veterans' family members to aid treatment effectiveness. A small, randomized, controlled trial is being conducted to examine the impact of a two-session family intervention to complement the delivery of Cognitive Processing Therapy (CPT) or PE. The goals of the intervention are to increase family members' support for and understanding of trauma-focused treatment, and also to reduce levels of family accommodation around PTSD symptoms.

In the area of complementary interventions, a continuing five-year study is examining the impact of two 12-week group treatments on chronic pain in Gulf War Illness. A one-year pilot study is examining the same interventions for older, sedentary, trauma-exposed Veterans. In both studies, tai chi, a mind-body exercise that has been associated with physical and mental health benefits, is compared with a wellness promotion intervention that is based on an existing VA model of care entitled Whole Health.

Division investigators also are examining a developmental phenomenon termed later-adulthood trauma reengagement (LATR). It involves efforts by older combat Veterans to actively re-engage with wartime memories with the aim of building coherence and finding meaning in past experience. It is theorized that the LATR process has the potential to lead to either positive outcomes such as personal growth or negative outcomes such as increased PTSD symptoms. An ongoing study is examining the impact of a 10-week psychosocial discussion group for older combat Veterans who report experiences consistent with the LATR process.

Division investigators are partnering with researchers in the Women's Health Sciences Division to examine the effects of trauma and other high-impact stressors on PTSD and related sequelae such as substance use disorders among lesbian, gay, bisexual, and transgender (LGBT) Veterans. This research aims to develop and refine conceptual models of trauma, PTSD, and related impairments to inform research, treatment development, and treatment planning for LGBT Veterans.

### **Care Delivery, Models of Care, and System Factors**

The main example of work related to this National Center priority is a project that examines how evidence-based psychotherapy (EBP) is delivered by clinicians affiliated with the VA Boston Healthcare System Outpatient PTSD Clinic. Findings indicate that strategic changes in clinic intake procedures, such as distributing materials describing treatment options and adding a second intake session focused on collaborative treatment planning, were associated with increased rates of retention in treatment for PTSD.

### **DSM-5**

Data collection is complete for a study validating a cutoff score for PTSD status according to *Diagnostic and Statistical Manual of Mental Disorders–Fifth Edition (DSM-5)* criteria based on the most recent version of the [Primary Care Screen for PTSD for DSM-5 \(PC-PTSD-5\)](#). The study is part of a larger effort to validate DSM-5 versions of measures that have been developed by National Center investigators. The ongoing project recruits Veterans from VA primary care

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locations and compares the screening measure to the gold-standard interview, the [Clinician-Administered PTSD Scale for DSM-5 \(CAPS-5\)](#). The study also examines the extent to which the optimal PC-PTSD-5 cutoff score varies across subgroups of Veterans. Data analyses have been completed and a manuscript is being prepared to submit for publication. A separate study co-led by a Division investigator aims to provide validation of CAPS-5 performance with a military sample.

### PTSD and Suicide

Division researchers are actively contributing to knowledge about PTSD and suicide, particularly in the domain of identifying risk factors. For one project, investigators used machine learning to identify the interactions among risk factors that predict future suicide attempts, using data from the Veterans After-Discharge Longitudinal Registry (Project VALOR) partitioned by gender. Results revealed that almost 8 percent of the sample made a suicide attempt over a five-year period. Machine learning partitioned by gender identified important similarities and differences in risk pathways.

Two other projects are testing interventions to prevent suicide among Veterans and Servicemembers who are at risk for suicide. One project will examine feasibility and acceptability of Brief Cognitive-Behavioral Therapy for suicide prevention in a sample of Veterans hospitalized for suicide risk. In addition, experience sampling will be used to explore granular fluctuations in suicide risk and related risk factors (e.g., hopelessness) during and after treatment.

In another project that was recently launched, in collaboration with the STRONG STAR (South Texas Research Organizational Network Guiding Studies on Trauma and Resilience) Consortium, Division investigators are testing a modified version of WET for Suicide with a sample of Army soldiers and Veterans with PTSD symptoms who have been hospitalized for suicide risk. The study seeks to determine whether treating PTSD symptoms reduces the likelihood of future suicidal behavior.

### Other Important Research

The Division has a great deal of expertise in longitudinal, observational studies that inform the understanding of the course of PTSD and associated conditions over time. Division researchers are working on two large prospective cohort studies that collect information from strategically selected Veteran and Servicemember groups. The first, [Project VALOR \(Veterans After-Discharge Longitudinal Registry\)](#), is working with a registry of 1,649 male and female combat Veterans who became users of VA services after 2002. The project collects data about health outcomes associated with PTSD, supplemented by clinical information from VA electronic medical records. Data collection for the fifth sampling wave is now complete, with over 1,000 participants providing saliva samples for future genomic analyses; examination of PTSD symptom trajectories and predictors of those trajectories are now complete.

The second large investigation, the [Neurocognition Deployment Health Study \(NDHS\)](#), began data collection at the outset of the Iraq War in 2003. Military personnel were assessed before deployment and at

several intervals afterward, making this the first prospective longitudinal study to address the psychological impact of war zone stress. The study design allows examination of long-term emotional and neuropsychological outcomes, as well as health-related quality of life and occupational functioning. Initial papers have described PTSD outcomes; longitudinal neuropsychological outcomes; and relationships among PTSD, TBI, and neuropsychological outcomes. Data preparation and analysis are underway for an associated study that examines the adjustment of both partners and children of the Servicemembers and Veterans in the cohort.

Using data from the Nurses' Health Study and VA Normative Aging Study, during which nurses and Veterans were followed for 10 and 30 years respectively, researchers found that higher initial levels of optimism were associated with 11 percent - 15 percent longer life span and 50 percent - 70 percent greater odds of achieving exceptional longevity, defined as reaching age 85.

In a related study examining psychosocial factors which underlie the associations of early experiences to longevity, investigators also found that greater optimism in midlife helped to explain the benefits of higher childhood socioeconomic status on greater longevity, whereas greater exposure to stressful life events in midlife accounted for some of the negative influence of childhood psychosocial stressors on reduced life span.

Division assessment research includes work with teams from the MITRE Corporation, a not-for-profit organization based in Bedford, Massachusetts, that manages federally funded

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research and development centers. The current project is aimed at developing a nonintrusive

method of PTSD detection based on voice analysis applied to interview recordings. This work identifies vocal markers related to timing and coordination of speech to determine the

presence and severity of PTSD. The nonintrusive nature of this approach increases its potential for real-world application; a patent application has been filed.

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## Clinical Neurosciences Division

*The Clinical Neurosciences Division in West Haven, Connecticut, focuses on research to establish novel treatments and uncover biomarkers of disease mechanisms related to traumatic stress, and investigates paradigms of risk and resilience. By leveraging an interdisciplinary approach that includes genetics, neuroimaging, treatment interventions, and epidemiological studies, the Division maximizes efforts to translate discoveries into therapeutic targets for PTSD and associated comorbid conditions*

### Biomarkers

Neurogenomics and neuroimaging drive biomarker development, including molecular, biochemical, structural, and functional approaches to investigate stress-related phenotypes and to better understand the sequence of pathological events associated with posttraumatic stress. The cross-cutting nature of this work provides a foundation to research methods for the early detection of at-risk individuals, genetic and environmental interactions underlying symptoms, and treatment response.

Division researchers use genome-wide association studies (GWAS) to screen for genetic variations across large numbers of research participants. GWAS data from 165,000 U.S. military Veterans participating in the [Million Veteran Program \(MVP\)](#) provided the first evidence of genetic vulnerability to one of the hallmark symptoms of PTSD, re-experiencing traumatic events. A report published in Nature

Neuroscience describes eight distinct genetic regions associated with PTSD and stress response: markers for genes that influence corticosteroid function (CRHR1 and HSD17B11), immune and inflammatory response (RAB27B), and associations with schizophrenia and bipolar disorder (TCF4 and MAD1L1). Genetic overlap between PTSD and schizophrenia may be due to shared biochemical pathways between hallucinations, dissociation, nightmares, and flashbacks, and may identify which PTSD patients are appropriate candidates for antipsychotic pharmacotherapy. Cell-type analyses revealed that medium spiny neurons may implicate striatal dysfunction in PTSD. Data further revealed that re-experiencing symptoms share genetic risk factors with hypertension.

The [VA National PTSD Brain Bank](#) studies postmortem brain tissue of PTSD and major depressive disorder (MDD) donors to characterize gene expression associated with stress and suicide, which may lead to blood-based biomarkers that could be used to diagnose and

monitor treatment response. RNAseq analysis, involving more than 1,900 tissue samples of cortical and limbic brain regions revealed patterns of gene co-expression, and sex-specific transcriptional changes in four regions of the prefrontal cortex.

Bioinformatic data suggest that endothelial cells, important in the transit of white blood cells; microglial cells responsible for activating inflammation; and neurons are co-regulated across PTSD. Consistent with GWAS data, transcriptomic signatures for PTSD closely resemble those of schizophrenia and bipolar disorder, suggesting a convergent pathology. Finally, transcriptomic studies of amygdala brain regions implicate microglial cells and astrocytes (i.e., glial cells which regulate transmission of electrical impulses in the brain) in the pathophysiology of PTSD.

Using data from the [National Health and Resilience in Veterans Study \(NHRVS\)](#), investigators examined genetic and epigenetic factors implicated in PTSD with an emphasis on how protective factors such as physical exercise and social support may moderate the deleterious effects of genes associated with PTSD. Data including the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism revealed that, among highly trauma-exposed “risk allele” carriers, those who engaged in physical

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exercise had substantially reduced risk of PTSD. Additionally, a study involving more than 1,135 U.S. Veterans looked at molecular DNA methylation factors associated with biological aging, and revealed that greater lifetime trauma exposure and childhood sexual trauma were associated with accelerated DNA aging.

Division researchers use multimodal neuroimaging, such as positron emission tomography (PET), MRI, and spectroscopy, to investigate functional activation patterns, concentrations of neurotransmitters, the structure and shape of brain regions, and energy demands throughout the brain. This work also includes large-scale mapping of the PTSD brain connectome, a brain circuitry map. Efforts continue to build a large neuroimaging data repository in order to develop machine learning and artificial intelligence methods.

Investigators also use electroencephalogram (EEG) to evaluate changes in electrical activity in the brain both before and after pharmacotherapy treatment. This year, the Division also acquired the first magnetoencephalography (MEG) unit within the VA health care system. MEG is a cutting-edge, highly sensitive technology with greater sensitivity than EEG. It is capable of high temporal resolution of electrical activity in deep brain structures and is an important investigative tool for next-generation PTSD research.

Building on postmortem and genetic data, PET researchers studied transcription levels of translocator protein (TSPO), a marker of microglial and inflammatory immune response,

to determine the relationship between TSPO, peripheral immune markers, and PTSD symptoms. TSPO was significantly lower in PTSD subjects compared to subjects without PTSD in the insula, ventromedial prefrontal cortex, and prefrontal-limbic regions. The latter region was also associated with lower IFN-gamma, a proinflammatory cytokine implicated in autoimmune disease, and with greater PTSD symptom severity. This study provided the first known in vivo evidence of neuroimmune dysregulation in PTSD.

PET researchers also examined synaptic density in PTSD and MDD using a new radioligand that quantifies synaptic vesicle protein (SV2A). This research demonstrated that severity of depressive symptoms is associated with lower synaptic density, as well as with disrupted connectivity. This finding was the first in vivo confirmation that depression is associated with altered synaptic density.

Five separate studies used MRI and computational modeling to examine PTSD-related brain dysfunction.

- ▶ A study using fractional anisotropy in PTSD subjects found altered white matter in the cingulum angular bundle, a brain region implicated in executive function and neurodegeneration.
- ▶ Researchers studied Veterans who are both apolipoprotein E (APOE) e4 allele carriers and have a diagnosis of PTSD, and demonstrated that they have significantly greater cognitive difficulties than e4 carriers without PTSD.
- ▶ An investigation of associative learning in

combat Veterans with severe PTSD found that two brain regions, the amygdala and striatum, are less able to track changes in threat level and demonstrated impaired learning, suggesting more difficulty in unlearning fear upon return to civilian life.

- ▶ An evaluation of a newly developed pupillary biomarker examined stress arousal via neuron firing in the locus coeruleus, a brain region that also controls changes in the pupil of the eye.
- ▶ A study using a novel calibrated functional MRI (fMRI) technique investigated trauma and mood symptoms under drug challenge with ketamine and perampanel.

### **Treatment Efficiency, Effectiveness, and Engagement**

NHRVS data was used to conduct the first known nationally representative study comparing Veterans use of VA as their primary source of health care. The study provides a comprehensive and up-to-date sociodemographic, military, and clinical profile of U.S. Veterans who do and do not utilize VA services.

Relative to non-VA users, VA users are more likely to be younger, female, Black, unmarried, less educated, and to have lower household incomes; they were also more likely to have served longer in the military and in combat roles. Looking at factors related to health, VA users were more likely to have lifetime psychiatric disorders, endorse current suicidality, report more trauma in their lifetimes, report more medical conditions, endorse a disability, and score lower on measures of functioning. The most important factor that differentiated VA health care users was

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*(Clinical Neurosciences Division, continued)*

the presence of a lifetime psychiatric disorder. The study suggests that Veterans who use VA health care have an elevated health burden; these findings may help inform outreach and engagement initiatives.

Division researchers are also conducting a number of treatment-based trials:

- ▶ A clinical trial of repeated doses of ketamine for treatment-resistant PTSD, with an added emphasis on durability of treatment response.
- ▶ A seven-day trial of PE enhanced with a single infusion of ketamine.
- ▶ A study of combined PE and CPT in VA PTSD residential treatment programs.
- ▶ A project examining Mindfulness-Based Stress Reduction for anger and aggression in Veterans with PTSD.
- ▶ An examination of chronic pain, anger, and aggression in PTSD using ecological momentary assessment (EMA).
- ▶ A trial of transcranial direct current stimulation on learning, memory, and brain circuitry.
- ▶ A trial of buprenorphine and CPT for patients diagnosed with PTSD and opiate use disorder; opiate use disorder is more common in diagnoses of PTSD.
- ▶ A study that examines the effect of WET in Veterans diagnosed with PTSD and comorbid substance use disorder.
- ▶ A study to examine the effect of sirolimus and

ketamine on neuroinflammation; this project expands upon previous work demonstrating prolonged remission with the combined treatments.

- ▶ A study of the neural and behavioral effects of serotonin-releasing agent 3,4-methylenedioxy-methamphetamine (MDMA) in PTSD.

The Division will also lead VA Cooperative Studies Program (CSP) #2016, targeting 1,224 patients at 34 VA Medical Centers. This study compares three commonly prescribed pharmacotherapies for insomnia: trazodone, gabapentin, and eszopiclone. Insomnia is among the most common persisting symptom of PTSD, with more than 80 percent of patients who are actively engaged in other behavioral and pharmacologic treatments reporting this symptom. At present, there are no medications approved for the treatment of PTSD-related insomnia.

### **DSM-5**

The Division has been involved in the National Center's efforts in development and validation of assessment instruments for *DSM-5*. NHRVS data was used to examine predominant typologies of *DSM-5* PTSD symptoms in the U.S. Veteran population. Results revealed three typologies of PTSD, differentiated by both the nature and severity of symptoms: Dysphoric (i.e., negative affect and anhedonic symptoms); High Symptom (i.e., high probabilities of all symptom clusters); and Threat (i.e., intrusive and avoidance symptoms).

These typologies differed in their clinical features. The Dysphoric group had higher rates of depression and substance use disorders

than the Threat typology. The High Symptom typology had higher rates across all disorders, including suicidality, relative to the Dysphoric and Threat typologies. These results underscore the importance of a personalized approach to the assessment, monitoring, and treatment of *DSM-5* PTSD, as well as the clinical burden of the High Symptom typology, in U.S. Veterans.

### **PTSD and Suicide**

Division researchers are investigating the use of pharmacological agents that have an acute antidepressant effect as a strategy to prevent suicide among individuals with PTSD. This work includes several projects that evaluate the anti-suicidal properties of ketamine in both treatment-resistant PTSD and depression, and how neural alterations and changes in synaptic connectivity both before and after ketamine treatment may underlie these behavioral changes.

Researchers are also developing a database of longitudinal factors related to suicidality, PTSD, depression, neuroimaging, and behavioral data to study symptom trajectory and outcomes over time. Other work includes a study examining PTSD, suicidality, and brain-based biomarkers in caregivers of Veterans with PTSD, using connectome-based predictive modeling to identify critical nodes and circuits that may predict the severity of suicidal behavior.

New findings involving the glutamatergic metabotropic receptor (mGluR5) were also uncovered. Using PET, researchers measured mGluR5 levels in individuals with PTSD and MDD who reported suicidal thinking at the time of scanning and found high levels of mGluR5 in the PTSD group with current suicidal thoughts.

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There were no elevated levels observed in the PTSD group without suicidal thoughts or in the MDD group, either with or without current suicidal thoughts. This work supports mGluR5 as a biomarker linked to PTSD-related suicidal ideation.

NHRVS data revealed a wealth of conclusions related to suicidality. Veterans with both PTSD and MDD are significantly more likely to have attempted suicide and to be currently contemplating suicide, compared to Veterans with PTSD or MDD alone. Anhedonic and externalizing symptoms of PTSD are most

strongly linked to suicidal thinking. Veterans who use VA as their primary source of health care have significantly higher rates of suicide attempts and suicidal thinking than those who do not. Factors such as greater purpose in life, curiosity, and optimism may help buffer the probability of suicidality in high-risk Veterans with histories of PTSD and depression. Finally, a greater sense of meaning in life moderates the relationship between suicidal ideation and experiences that violate the person's moral or ethical standards.

Published NHRVS study findings documented the effect of homelessness on suicidality, showing that Veterans with a history of homelessness are five times more likely to attempt suicide

than those with no such history. These findings made an immediate translational impact on policy, as directives were issued on roles and responsibilities of VA homeless programs in suicide prevention.

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## Dissemination and Training Division

*The Dissemination and Training Division in Palo Alto, California, conducts research on patient needs and preferences, implementation science, the development of novel and adapted treatments that attend to patient preferences, and the development and testing of technology-based delivery of treatment.*

### Treatment Efficiency, Effectiveness, and Engagement

A key focus of Division researchers is increasing patient engagement into care. One study is developing a brief measure of patient characteristics associated with effective engagement in care, which will guide identification of the type and amount of service resources needed to engage Veterans. A second study is focusing on racial and ethnic minority patients who have been found to experience disparities in trauma exposure and mental health care. The project will develop a screening tool

that identifies patients at risk for subsequent mental health problems and identify resources tailored to particular patient problems and needs to increase engagement into care.

Several ongoing studies are assessing the ability of web-based and mobile technologies to increase Veteran access to mental health care and to enhance outcomes. Telemental health services in the home are expected to increase patient engagement and access, but to date this type of service has rarely been implemented. A hybrid effectiveness and implementation study will compare two treatments delivered to women

Veterans in their homes via video teleconference: Skills Training in Affective and Interpersonal Regulation (STAIR) and Present-Centered Therapy (PCT). The goals of the study are to assess the relative effectiveness of these treatments and to identify barriers and facilitators for using video for home delivery treatment.

The efficacy of web-PE, a web version of PE, in reducing symptoms of PTSD in military personnel and Veterans is being tested. Web-PE is delivered online with therapist oversight and facilitation, and could have significant potential to increase the reach of PE to those who cannot otherwise access traditional face-to-face care. A new study will test whether the addition of peer support increases adherence to and completion of online treatment. This trial will compare patient engagement and outcomes from using Moving Forward, a VA online version of Problem Solving

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*(Dissemination and Training Division, continued)*

Therapy, with and without peer support.

A two-site study is underway to assess the efficacy of PTSD Coach compared with traditional treatment for reducing PTSD symptoms in Veterans utilizing primary care services. Several pilot studies of mobile phone apps are near completion, including a pilot study of app-based personalized and semiautomated coaching integrated into PTSD Coach; a pilot study of a couples-based intervention using mobile apps; and two ongoing trials of the Mindfulness Coach app in Veterans with PTSD and as an adjunct for Veterans receiving other types of medical care.

A mobile cognitive control training for the treatment of alcohol use disorder (AUD) and PTSD will determine the efficacy of a novel neurocognitive intervention for improving recovery outcomes. The National Center and the VA Palo Alto Health Care System received funding for a Center for mHealth Applications Research, Resources, and Services to aid mobile health research by National Center and other VA investigators.

In collaboration with researchers from the Minneapolis VA Health Care System, the Division is conducting a study to test a web-based intervention to help National Guard families encourage their loved ones to seek mental health care. Key questions concerning the methods and the extent to which social networks can be utilized to increase treatment engagement, and to improve mental and physical health outcomes, are being investigated in a study of cancer survivors, another highly stressed population.

### Care Delivery, Models of Care, and System Factors

New efforts are underway to improve patient access to care by using participatory systems dynamics modeling, a collaborative quality improvement approach in which stakeholders identify specific system problems, use computer modeling to compare the likely outcomes of different potential solutions, and then select an optimal solution to implement. Preliminary pilot data indicate substantially improved access to evidence-based psychotherapy (EBP) at two facilities using this method.

Technical Assistance Specialists in the VA Office of Mental Health and Suicide Prevention have been trained in this approach and are partnering with the National Center in two studies. These randomized controlled trials will test the effects of participatory systems dynamics modeling on increasing provision of evidence-based treatments, its mechanisms of action, and its cost-effectiveness relative to usual VA quality improvement.

### Implementation

A study evaluating how to simplify assessment of the quality of delivery of cognitive-behavioral therapy (CBT) for PTSD, depression, and anxiety disorders is underway. A second ongoing study is evaluating competing strategies intended to enhance and sustain the delivery of CPT; one strategy emphasizes fidelity to the protocol through expert consultation and online resources, and the other focuses on using continuous quality improvement strategies to improve fit and to address barriers to treatment delivery.

Investigators involved in the evaluation of the national rollout for PE are studying the effectiveness of different training models on trainee delivery of PE. Another study compares methods of assessing treatment quality and fidelity, two important implementation outcomes for CBTs, including CPT. National Center staff are also supporting VA's efforts to implement measurement-based care (MBC), and recently published results of three qualitative studies on implementation of MBC.

In collaboration with the Minneapolis VA Health Care System, investigators at two National Center Divisions are testing an implementation toolkit and facilitation to increase use of EBPs in VA PTSD clinics. This project leverages findings from a prior study on organizational factors that contribute to wider use of EBPs, and is now being extended to Department of Defense (DOD) clinics in a multi-site trial involving collaborators from five universities and eight military bases. The study will assess whether a tailored approach combining an implementation toolkit, a rubric for matching solutions to local barriers, and support from an external facilitator increases the use of PE more than standard provider training alone.

### PTSD and Suicide

Division staff are working on developing participatory system dynamics modeling tools that clinic teams can use to optimize and allocate staff resources to different clinical activities. These tools are now being expanded to suicide management to help teams ensure effective management of Veteran patients at high risk for suicide, without compromising overall access to or quality of care.

## Evaluation Division

*The Evaluation Division in West Haven, Connecticut, supports the National Center's mission through a programmatic link with VA's Northeast Program Evaluation Center (NEPEC). NEPEC has broad responsibilities within the VA Office of Mental Health and Suicide Prevention (OMHSP) to evaluate their treatment programs, including those for specialized treatment of PTSD. Although researchers are primarily engaged in evaluation research, they also work on independent research projects related to the treatment of PTSD.*

### Biomarkers

Dr. Matthew Friedman, Senior Advisor to the National Center, continues to coordinate the operations of VA's first [National PTSD Brain Bank](#). The PTSD Brain Bank supports the Presidential Executive Order of August 2012 on deployment health by enabling VA to lead the nation in unique research that will facilitate deeper understanding of the causes and consequences of PTSD, as well as advancing assessment and treatment techniques.

The PTSD Brain Bank has seven parts, with facilities at five VA Medical Centers (Durham, North Carolina; Boston, Massachusetts; Waco, Texas; West Haven, Connecticut; and White River Junction, Vermont), the University of Miami, and the Uniformed Services University of the Health Sciences. The Clinical Neurosciences Division in West Haven is the primary data analysis site; ongoing research endeavors utilizing PTSD Brain Bank tissue are described in the Clinical Neurosciences Division narrative.

As of the end of FY 2019, the PTSD Brain Bank had 260 PTSD and comparison frozen hemispheres (roughly one-third each from donors with PTSD, donors with major depression, and healthy controls). In addition, the PTSD Brain Bank has 22

fixed hemispheres. An additional 100 prospective tissue donors have volunteered to be followed over their lifetimes. There has been considerable progress on major projects regarding bulk and single cell RNA sequencing and DNA methylation from key brain areas, including a collaboration with the Lieber Institute for Brain Development that will obtain transcriptomic data from eight brain regions from over 300 brains, divided between PTSD, major depressive disorder (MDD), and healthy controls.

The biomarkers portfolio also includes examinations of biomarkers of treatment response and neuroimaging research. Transcranial magnetic stimulation (TMS) is a device-based, FDA-cleared intervention for depression that is being tested as a treatment for PTSD. Executive Division investigators are currently examining EEG and fMRI biomarkers of response to TMS among Veterans with treatment-resistant depression.

The first study of the neural correlates of social working memory in PTSD completed recruitment. Interim analyses suggest that individuals with PTSD have more difficulty than trauma-exposed comparison participants with maintaining and manipulating social information on a moment-

to-moment basis. An ongoing study is using EEG, eye tracking, and behavioral measures to examine the interaction between emotional processing and attentional functioning in healthy adult participants and trauma-exposed individuals with and without PTSD.

### Treatment Efficiency, Effectiveness, and Engagement

The Executive Division has a long history of participation in VA's CSP. During FY 2019, CSP #591, a groundbreaking study comparing PE and CPT at 17 VA facilities across the country, was completed. The investigators enrolled 916 participants, more than the 900 that were anticipated, and data analysis is projected to be completed by the second quarter of FY 2020. Findings will help VA leadership, clinicians, and Veterans make informed choices about the delivery of PTSD care in VA, and will also be broadly relevant to the scientific and clinical communities outside VA.

The National Center previously developed [AboutFace](#), a public awareness campaign to help Veterans recognize PTSD and motivate them to seek treatment. Recruitment for a project in which investigators are examining the impact of AboutFace on engagement in and completion of evidence-based treatment among Veterans with PTSD is ongoing. They will also examine the impact of AboutFace on stigma and attitudes toward mental health services.

Investigators continue to focus on treatments for conditions that frequently co-occur with PTSD and to examine novel treatments for PTSD.

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The primary outcomes for a trial comparing two psychotherapies for comorbid AUD and PTSD (PE and Seeking Safety) were published in JAMA Psychiatry in FY 2019. Recruitment for a trial that is evaluating the combination of topiramate and PE for co-occurring PTSD and AUD is ongoing.

Results from a pilot study investigating the safety and efficacy of a novel form of synchronized TMS for PTSD with comorbid depression were published. The first study of cannabidiol-enhanced PE in Veterans launched in FY 2019, with the first participant enrolled in May 2019. Lastly, a trial to evaluate a brief protocol to reduce guilt and shame related to a traumatic event among Veterans of Iraq and Afghanistan will be finishing recruitment in early 2020.

During FY 2019 the National Center partnered with the Agency for Healthcare Research and Quality to create the [PTSD Trials Standardized Database Repository \(PTSD-Repository\)](#), a large database of PTSD clinical trials. The data were generated from a systematic review of 318 published trials of PTSD interventions. Data are freely available to researchers, clinicians, and other stakeholders. This online repository will inform future study design and conduct and will aid researchers and policymakers in identifying important gaps in the research.

### Care Delivery, Models of Care, and System Factors

The Executive Division is working on several initiatives aimed at assessing models of care and improving evidence-based practices.

Investigators continue to analyze data from a national survey that assessed the treatment needs and preferences of Veterans and non-Veterans with PTSD symptoms and informed the development of the [PTSD Treatment Decision Aid](#). This is the first publicly available online treatment decision aid for PTSD, and it has received more than 250,000 views since its release in 2017.

Most recently, investigators published results of a qualitative investigation of PTSD treatment preferences among adults with PTSD symptoms. The study found that preferences were shaped by factors such as perceived treatment effectiveness, familiarity with the treatment, and delivery format. By highlighting which pieces of information may be most important to detail when presenting different treatment options, these results can help guide treatment planning conversations, as well as the development of decision-support tools.

Executive Division investigators continue to examine the impact of facilitation and academic detailing, in which a pharmacist and psychologist reach out directly to VA clinicians in rural clinics to improve PTSD treatment practices. An ongoing initiative is focused on sharing guideline-recommended practices for PTSD with rural facilities outside New England. Innovative natural language processing methods were used to identify rural sites across the country that were low in delivery of evidence-based treatments.

Two new projects will begin in FY 2020. The first aims to improve access to evidence-based treatments for Veterans with PTSD at rural facilities utilizing facilitation, academic detailing, and collaboration with the National

Center's Mentoring Program. Expansion will include measuring the sustainability of the implementation work done in FY 2019. The second initiative will create a collaboration with the team's local Office of Community Care to identify providers in the area who are planning to treat Veterans through the MISSION Act, which allows Veterans to access care in the community. The project will also create a streamlined network with local community providers to enhance their knowledge of the 2017 VA/DOD PTSD Clinical Practice Guideline (CPG) treatment recommendations and share current best practices regarding suicide risk assessment.

In addition to projects aimed at improving clinical practices, investigators are continuing to assess the state of care for PTSD in VA using novel informatics and operational methods. In FY 2019, investigators completed work to derive outcome-based quality standards for use of EBPs and evidence-based antidepressants (EBAs, including fluoxetine, sertraline, paroxetine, and venlafaxine) over a 10-year period of observation using VA medical records data. There was a steady increase in the use of PE and CPT but little change in the use of EBAs. However, when the most rigorous quality standards were applied, the team identified significant opportunities for improvement of both EBPs and EBAs. Proposals in development will seek to address these gaps in a targeted data-driven manner. Ongoing work in this area includes funded work to compare the effectiveness of EBAs in routine practice.

### DSM-5

In collaboration with the Behavioral Science Division, the Executive Division is leading a study

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*(Evaluation Division, continued)*

to provide further validation of the [PC-PTSD-5](#), which is currently used across VA for mandatory PTSD screening. Although initial validation has been completed, the ongoing study, which uses the [CAPS-5](#) as the criterion index, will provide more definitive information regarding the most appropriate cutoff scores and will allow investigation of the screen's ability to detect PTSD in key subgroups such as women. Data analyses have been completed and a manuscript is being prepared to submit for publication.

### PTSD and Suicide

Executive Division researchers continue to advance the priority area of PTSD and suicide through collaborations with the National Center for Patient Safety (NCPS), OMHSP, and the Center of Excellence (COE) for Prevention of Suicide.

Recently completed work with this COE shows potential misclassification in suicide outcomes across data sources available to VA operations and researchers. A separate study using semantic analysis of clinical note text to evaluate ruptures in therapeutic alliance preceding death by suicide

in a VA PTSD treatment population is nearing completion. A new study that will launch in FY 2020 will leverage an existing 10-year national longitudinal cohort of VA users to answer important questions about rural-urban differences in death by suicide. Finally, based on previous work showing elevated risk of suicide during high-risk care transitions, investigators will develop and implement an effective suicide prevention intervention for rural VA facilities to decrease suicide risk in Veterans living in rural settings.

## Pacific Islands Division

*The Pacific Islands Division in Honolulu, Hawaii, was created to advance PTSD work in the Pacific Rim; to focus on improving access to care by increasing understanding of cultural attitudes and the bases of racial and ethnic disparities in treatment; and to evaluate the use of advanced technology, such as telemedicine, to reach out to Veterans who are otherwise unable to access adequate care.*

### Treatment Efficiency, Effectiveness, and Engagement

Three major projects are aimed at evaluating different methods of delivering PTSD treatment. Investigators are in the final phase of a large trial that examined Veterans' preferences for and the clinical efficacy of three modalities for the provision of PE: two involving technology and one involving in-home visits to Veterans. A second trial is comparing different treatments for in-home delivery of a couples-based intervention for PTSD; this study examines the clinical efficacy of brief Cognitive-Behavioral Conjoint Therapy (CBCT) and compares home-based care to traditional office-based care. A

new trial in collaboration with the Dissemination and Training Division is looking at home-based STAIR treatment for women Veterans who have experienced MST. The third study, a collaboration with investigators at the Minneapolis VA Health Care System, is a multi-site trial comparing standard PE with PE incorporating a partner.

### Other Important Research

Several ongoing studies examine the prevalence of PTSD, response to treatment, and presence of related mental health comorbidities in ethnic minority populations. These studies identify unique risk and resilience correlates of PTSD among ethnically and racially diverse Veterans,

and the effects of those correlates on Veterans' response to evidence-based PTSD treatments.

Researchers are continuing a study initiated in FY 2017 that uses data from the Honolulu Asian-Aging project to look at the effects of military service combat exposure in particular on late-life dementia, as well as on marital and family structures, mental health, and physical health among Japanese-American men.

An ongoing project conducted in conjunction with the Military Family Research Institute at Purdue University examines sociocultural and community influences on mental health decision-making among male and female African-American, Asian-American, Latino, and non-Latino white Veterans who are starting PTSD care in a VA mental health clinic. This mixed-methods study uses qualitative phone interviews, follow-up surveys, and census information. Part one of the interview examines who in their social networks Veterans talk to about mental health

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*(Pacific Islands Division, continued)*

problems and treatment, how much they value that input, and why. Other parts of the interview and the follow-up survey examine experiences with and conceptualization of PTSD, treatment, and treatment providers.

The Division is also working on a national qualitative study examining dropout from evidence-based treatments, in collaboration with investigators from the Women's Health Sciences Division and Minneapolis Health Services Research & Development Center of Innovation. Finally, a statistical methodology project is

underway to develop an estimation method to delineate individual factor contributions in observational studies, where models include functional data as either an outcome or as one of a large number of covariates.

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## Women's Health Sciences Division

*The Women's Health Sciences Division in Boston, Massachusetts, specializes in the study of women Veterans and non-Veterans, with a particular focus on understanding gender differences in trauma exposure and posttrauma psychopathology.*

### Biomarkers

Research on biomarkers includes studies aimed at explaining the basic biological processes underlying PTSD with particular relevance to women. One study is examining the role of neurobiological and psychosocial factors that affect negative pregnancy outcomes among women with PTSD. Another is performing data analysis on a study of sex hormones and derivatives associated with decreased retention of extinction learning across the menstrual cycle in women with PTSD. A third is a study of GABA-ergic neuroprotective steroids in men and in women across the menstrual cycle. Recently published results reveal that deficient activity among enzymes converting progesterone to its anxiolytic metabolites is related to PTSD severity for both men and women, but that the site of this deficiency is different among women. This suggests that sex-specific treatments for correction of the deficiency may be needed.

Studies examining the role of biomarkers in intervention efforts include the initiation of a new study investigating whether a specific electrophysiological response pattern to a series of loud tones is predictive of clinical responses to selective serotonin reuptake inhibitors (SSRIs). Investigators are also working on a series of studies looking into the role of progressive exercise training to reduce chronic pain and PTSD symptoms, perhaps by improving participants' capacity to release stress and pain-reducing neurohormones.

Division researchers are also seeking to pioneer scientific inquiry in the area of head injury in women suffering from PTSD secondary to IPV. The aim is to understand the interactive biological and psychological mechanisms that underlie comorbid PTSD and TBI. One key objective is to begin to develop multimodal treatments for comorbid PTSD and TBI that would be more effective than current, single-modal strategies. Investigators will be able

to examine sex differences across domains of measurement (psychiatric, psychosocial, neuropsychological, blood-based biomarkers, and imaging) by comparing this sample with comparable male samples.

### Treatment Efficiency, Effectiveness, and Engagement

Several intervention studies are examining more efficient and effective treatment modalities for delivering CPT. With support from the [STRONG STAR Consortium](#), investigators are continuing to analyze data from a study comparing the relative effectiveness of CPT delivered in an individual format with that delivered in a group format.

Also through STRONG STAR, staff are investigating a variable-length CPT protocol, testing the efficacy of the intervention when treatment end is determined by patient progress. Another trial is testing the efficacy of CPT delivered in an intensive outpatient format with active-duty Servicemembers. This one-week version of CPT is also being piloted in female survivors of IPV with PTSD and traumatic brain injuries (TBIs).

In the area of treatment effectiveness, investigators are working to improve adherence to existing PTSD treatments. A recently

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*(Women's Health Sciences Division, continued)*

completed study explored Veteran and provider perspectives on reasons for dropout from both CPT and PE in order to develop an intervention aimed at increasing rates of completion for these treatments. Another recent study focused on improving the assessment of sleep impairment in the context of PTSD via objective measures, self-report global measures, and daily symptom monitoring diaries; researchers hope that therapy might better target trauma-related insomnia, the most-often reported symptom of PTSD and, arguably, the most resistant to treatment. Other intervention studies on traumatized populations include an open trial to test the effectiveness of a therapist-assisted self-management intervention intended to increase self-efficacy and facilitate greater community engagement following a successful course of PTSD treatment.

The Division is also focused on intervention research among those who have not necessarily been diagnosed with PTSD. Researchers are looking into the effectiveness of a national network of peer-facilitated support groups for women Veterans, titled [WoVeN: The Women Veterans Network](#), which is intended to increase social connections and support and to improve well-being. In addition to ongoing effectiveness evaluations, recent efforts have focused on the implementation of a train-the-trainer model to facilitate the dissemination of these peer-facilitated support groups.

Treatment engagement research includes studies of subpopulations of interest. Division researchers recently published findings about the experience of seeking PTSD treatment in a sample of

discrimination-based-trauma-exposed lesbian, gay, bisexual, and transgender (LGBT) Veterans. This work led to a new model for conceptualizing trauma recovery among sexual and gender minority people that considers their unique minority context and ongoing exposures. Current work is further refining this new model for conceptualizing the sequelae of discrimination, minority stress, and microaggressions among transgender trauma survivors.

### Care Delivery, Models of Care and System Factors

The Division's focus on care delivery emphasizes care for conditions with particular relevance to women Veterans. One mixed-methods study is looking at Veterans' experiences with and preferences for communication with Veterans Health Administration (VHA) providers about MST. Investigators interviewed male and female Veterans, including Veterans who had experienced MST and those who had not, to ask about their experiences. Veterans from all groups reported generally high satisfaction with MST-related communication, although men, as a group, reported a much larger range of satisfaction ratings than women.

Two studies are investigating VHA health care use related to eating disorders, in a nationally representative sample of male and female Veterans and a large cohort of post-9/11 male and female Veterans. These investigations will also look to identify barriers to mental health care use, both in general and specifically related to eating disorders.

Other studies have focused on understanding

patterns of service use among post-9/11 Veterans. The [Veterans Metric Initiative](#) is a large-scale longitudinal study investigating newly separated Servicemembers' reintegration experiences and use of transition programs, services, and supports. Comparisons between female and male Veterans at the time of separation suggest that female Veterans experience unique areas of risk and resilience. Risk factors include greater likelihood of experiencing depression and anxiety, as well as slightly lower resilience, reflected in the ability to bounce back from adversity. Resilience factors include better parental functioning, less tobacco use, and greater likelihood of seeking needed care.

Investigators also continue to analyze data from a study of the effects of deployment stressors and resulting mental health conditions on Veterans' quality of life and health care use. A key focus of recent analyses was the relationship between Veterans' functioning and their service use; findings suggest that functional impairments may serve as a facilitator of treatment seeking for women, whereas it may impede treatment seeking for men. Recent findings also highlight the importance of attending to the role of family stressors experienced during deployment on Veterans' longer-term mental health and corresponding needs for clinical services.

The health of older women Veterans is another area of focus. One study is examining the impact of military and other lifetime stress exposures and mental health results, with a focus on PTSD, later-life health and related quality of life in Vietnam-era women Veterans. Recent findings highlight the lasting impact of wartime stress exposures — including mission-related stressors and sexual discrimination and harassment — as

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*(Women's Health Sciences Division, continued)*

well as the roles of PTSD, depression, and anxiety on later-life functioning and disability. A second study, in collaboration with investigators from the Behavioral Science Division, is examining predictors of mortality, as well as changes in physical and mental health-related well-being over time, among female and male Vietnam-era Veterans.

### Implementation

Division investigators are conducting a range of implementation studies focused on identifying and disseminating best practices for IPV identification, assessment, treatment, and the targeting of health services within the VHA context. Division investigators are involved in planning and evaluating a national rollout of IPV screening programs within primary care clinics. As many as 20 VA Medical Centers will participate in an implementation-effectiveness randomized program evaluation that will determine the impact of the Office of Women's Health Services efforts on implementation outcomes (i.e.,

adoption, penetration, implementation fidelity, and sustainability) and the clinical effectiveness of IPV screening programs on disclosures and post-screening psychosocial service use.

In the area of implementation of interventions associated with IPV, researchers recently began a multi-site effectiveness-implementation clinical trial of a brief counseling intervention for women who are experiencing violence in their intimate relationships. This study incorporates a hybrid methodology to inform both the effectiveness of the intervention and expansion of the intervention throughout VA.

Investigators are applying implementation science to other issues of relevance to the National Center. One effort is examining Written Exposure Therapy (WET), a brief PTSD treatment, for pregnant women with comorbid PTSD and substance use disorder who are engaged in prenatal care within a high-risk obstetrical and addiction recovery program; the project is using a hybrid effectiveness-implementation design. Additionally, investigators are initiating a qualitative study to assess practices, attitudes, and strategies for increasing use of evidence-

based psychotherapies for mental health conditions in community-based outpatient clinics.

### PTSD and Suicide

The Longitudinal Investigation of Gender, Health, and Trauma (LIGHT) study is a national survey of Veterans living in high-crime neighborhoods, focusing on more clearly delineating the impact of trauma and community violence on mental, physical, and reproductive health and suicidal behavior among both women and men. To date, investigators have gathered data from over 3,500 Veterans, about half of whom are women, at an initial time point and are in the process of completing a second wave of assessments. With two more intervals of follow-up surveys planned, the complete study will include a total of four assessments over 18 months.