

# Appendix B:

## Fiscal Year 2018 Research Narrative

### Behavioral Science Division

The Behavioral Science Division in Boston, Massachusetts, conducts research on life adjustment after military deployment, 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 2018, Division investigators have focused on the role of inflammation and oxidative stress in the biology of PTSD, and on the role of PTSD 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. They also address long-term negative consequences such as neurodegenerative disease. The biomarkers examined by Behavioral Science Division studies include brain features measured by neuroimaging, as well as specific genes, polygenic risk scores, and epigenetic indicators drawn from both blood and brain tissue. New work is examining blood-based biomarkers associated with neuronal injury and inflammation.

During fiscal year (FY) 2018, Division investigators continued to use functional and structural magnetic resonance imaging (MRI) to identify neural circuitry involved in PTSD, particularly as related to memory suppression and emotion regulation.

#### PTSD and Suicide

Behavioral Science Division investigators are actively contributing to knowledge about PTSD and suicide, particularly in the domain of identifying risk factors for suicide. For one project, investigators are using machine learning to identify the interactions among risk factors which predict future suicide attempts using data from the Veterans After-Discharge Longitudinal Registry (Project VALOR), partitioned by gender. Specifically, risk factors assessed at baseline (e.g.,

PTSD diagnosis, TBI, prior suicide attempts) will be examined separately among male and female Veterans in predicting suicide attempts over the course of the 4.5 years of VALOR.

Another project aims to examine the degree to which risk factors vary in their association with future suicide attempts across demographically distinct groups. Mixture modeling was used to identify demographically homogenous groups using age, gender, race, household income, employment status, marital status, education level, and parental status. Investigators found five groups, across which there was great variability in the association between risk factors and future suicide attempts, thereby providing strong support for the idea that risk factors function very differently for different demographic groups. History of a prior suicide attempt emerged as the only significant predictor in all groups.

#### Treatment Efficiency, Effectiveness, and Engagement

Division investigators conduct pioneering research on treatments for PTSD, guided by the key aims of overcoming barriers to seeking care, reducing dropout, and increasing the efficiency of care delivery. One example is the internet-based treatment [VetChange](#), which is 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. The research version of VetChange was subsequently modified to include a mobile-friendly public website. This version, which is applicable to Veterans of all eras, is now under evaluation. A [mobile app](#) that has key VetChange features was recently developed in conjunction with the Dissemination and Training Division and will soon begin a pilot test phase. 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 clinics.

Other Division efforts include developing and testing efficient, therapist-delivered interventions or treatment extenders, with the goals of finding approaches that require less professional

(Behavioral Science Division, continued)

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 previously showed strong effects with non-Veteran patients. A high-profile study that was published in 2018 demonstrated that this brief intervention is as effective as Cognitive Processing Therapy (CPT), has a lower rate of dropout than CPT, and can be implemented successfully with Veterans.

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 are being implemented across the VA health care system and on one military installation. A new pilot study also is testing one of these programs in an underserved urban civilian setting.

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. Tai Chi, a mind-body exercise that has been associated with both 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 reengage with wartime memories with the aim of building coherence and finding meaning in past experience. It is theorized that the LATR process has 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.

#### 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. Initial 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 EBPs for PTSD.

#### DSM-5

Data collection is nearly complete for a study designed to validate 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 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. A separate study co-lead by a Behavioral Science Division investigator aims to provide validation of CAPS-5 performance with a military population; validation with a VA sample was completed previously.

#### Other Important Research

**Prospective cohort studies.** Division researchers are working on two large prospective cohort studies that collect information from strategically selected Veteran and Servicemember groups over time. The first, [Project VALOR](#), 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 fourth sampling wave is now complete, with 1,205 participants (73% of the initial cohort); examination of PTSD symptom trajectories and predictors of those trajectories are in process. The next phase of the project involves collecting saliva samples from participants for future genomic analyses.

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 it 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.

**Assessment.** Division assessment research includes work with teams from the MITRE Corporation and Massachusetts Institute of Technology Lincoln Laboratory to develop a noninvasive 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 noninvasive nature of this approach increases its potential for real-world application.

(Behavioral Science Division, continued)

Another ongoing project is closely aligned with the [VA National PTSD Brain Bank](#). The aim is to demonstrate optimal sources of information gathering related to brain donors who could not be interviewed prior to death. For this study, direct information is collected from living elderly Veterans to determine their diagnostic status for PTSD and related

mental disorders. This information is then used as the point of reference for comparison with indirect sources of information obtained by interviewing a close informant and examining the Veteran's medical record. The goals are to determine the best predictors from indirect sources and to provide guidance for information gathering by the PTSD Brain Bank.

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## Clinical Neurosciences Division

The Clinical Neurosciences Division in West Haven, Connecticut, focuses on research designed to establish novel treatments and uncover biomarkers of disease mechanisms related to traumatic stress, as well as research that investigates paradigms of risk and resilience. The Clinical Neurosciences Division utilizes an interdisciplinary approach that includes treatment interventions, neuroimaging, genetics, and epidemiological studies targeted at translating discoveries into therapeutic targets for PTSD and comorbid conditions.

### Biomarkers

Clinical Neurosciences Division investigators are working to characterize biochemical, structural, and functional abnormalities underlying PTSD; to elucidate brain, genetic, and environmental interactions that may affect symptom expression, treatment matching, and treatment response; and to investigate the effects of drug-induced alterations in brain and neurochemical functioning. This multifactorial pursuit of biomarker identification may lend insight into early detection of at-risk individuals and personalized or new therapeutic approaches for PTSD.

The Clinical Neurosciences Division utilizes neurogenomics to explore interactions among genotypes, phenotypes, and the environment via state of the art approaches. This work includes significant progress from the VA National PTSD Brain Bank, which conducted large postmortem analyses and next generation sequencing, characterizing altered gene expression in five different brain regions in subjects with PTSD and major depressive disorders. A unique bioinformatic pipeline has been developed within the PTSD Brain Bank to identify gene expression patterns within and between brain regions. Analyses revealed increased neuroinflammatory signaling, as well as cell adhesion and cell proliferation in these pathways. Previous work from the PTSD Brain Bank demonstrated that a specific gene, serum/glucocorticoid regulated kinase 1 (SGK1), was dramatically decreased in the prefrontal cortex of postmortem PTSD samples. Efforts to study the functional consequences of this gene alteration, such as fear memories and fear extinction, is continuing in animal models. Investigators are also evaluating strategies for raising SGK1 levels in the brain as a potential new treatment. Several other genes of interest, including *FKBP5* and *NPAS4*, have also been targeted to detect RNA expression in subjects with PTSD.

Data from the National Health and Resilience in Veterans Study ([NHRVS](#)), which surveyed a nationally representative sample of U.S. military Veterans, revealed that Veterans having

both high levels of trauma exposure and a genetic variation implicated in Alzheimer's disease (i.e., the apolipoprotein E [APOE]  $\epsilon 4$  allele carrier risk genotype) reported greater severity of PTSD symptoms, particularly re-experiencing symptoms. APOE  $\epsilon 4$  allele carriers who reported both more trauma as well as higher levels of social support were less likely to screen positive for PTSD. Researchers also examined a variation in the neuropeptide Y gene (promoter rs16147) which has been shown to impact resilience to traumatic stress. Results revealed that Veterans with the "protective" genotype (T/T homozygotes) showed greater resilience to developing PTSD symptoms, particularly intrusion symptoms, even with increased levels of lifetime trauma. Investigators also continued to participate in the Million Veteran Program ([MVP](#)), where genome-wide analysis work with PTSD participants is in progress. Collaboration also continues with the PTSD PGC Workgroup and with the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS) consortium.

Clinical Neurosciences Division investigators utilize non-invasive multimodal neuroimaging methods, such as MRI, magnetic resonance spectroscopy, and positron emission tomography (PET) to investigate the structure and shape of various brain regions, functional activation patterns in gray matter, the integrity of white matter tracts, concentrations of neurotransmitters and other chemicals in the brain, as well as energy demands and usage throughout the brain. Investigators also use electroencephalogram (EEG) to evaluate changes in electrical activity in the brain pre/post ketamine treatment among patients with treatment-resistant PTSD.

Current PET research focusing on the  $\alpha 7$  nicotinic acetylcholine receptor (nAChR), which can "tune" signaling in brain circuitry, has revealed reduced  $\alpha 7$  nAChR levels in the amygdala and hippocampus of individuals with PTSD. Ongoing work is investigating the role of the  $\alpha 7$  nAChR as a potential biomarker and/or treatment target for PTSD. Investigators are also evaluating the role of enzyme 11beta-hydroxysteroid

(Clinical Neurosciences Division, continued)

dehydrogenase 1 (11beta-HSD1), which activates the stress hormone cortisol, in PTSD. Preliminary data suggests that individuals with PTSD have higher levels of 11beta-HSD1 in the medial prefrontal cortex and hippocampus. Other ongoing PET work is examining changes in dopamine levels in trauma-exposed healthy individuals who use cannabis to determine whether changes in dopamine after smoking cannabis are associated with changes in stress-related symptoms. Investigators also continue to study neuroinflammatory processes in PTSD using PET technology. Prior work indicated a link between immune alterations and PTSD following trauma exposure. Researchers are investigating whether activation of microglial cells (i.e., cells which affect immune response in the central nervous system) contributes to a neuroinflammatory etiology of PTSD.

Investigators are using a drug challenge approach with guanfacine and perampanel to better understand how  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors affect trauma and mood symptoms. Results to date indicate that guanfacine alters the functioning of the prefrontal and locus coeruleus brain regions during tasks of cognitive performance.

Finally, work examining the neural basis of decision making under conditions of risk and uncertainty continues to identify biomarkers related to fear extinction, such as activity in the ventromedial prefrontal cortex (vmPFC). Functional MRI (fMRI) findings revealed reduced activity in the vmPFC of PTSD brains, with numbing symptoms significantly predicting neural activation. Additional work to pursue biomarkers related to fear learning was conducted using pupil dilation and study of cannabinoid receptor type 1 availability to examine individual differences as predictors of fear acquisition and extinction.

### **PTSD and Suicide**

Clinical Neurosciences Division investigators are using PET technology to examine availability of metabotropic glutamate receptor type 5 (mGluR5), which has an important role in fear learning and emotion regulation, as a potential biomarker for suicidal ideation. Results revealed that individuals with PTSD had higher mGluR5 availability relative to those with major depression in multiple frontal and limbic brain regions. In PTSD individuals, mGluR5 availability was also positively correlated with avoidance, tension, and anxiety, as well as same-day suicidal ideation, effects not observed in those with depression. These findings suggest that mGluR5 may be a potential treatment target.

Clinical Neurosciences Division researchers are also 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 pre/post ketamine, with emphasis on synaptic connectivity, may underlie these behavioral changes.

In other work, NHRVS data revealed that moral injury was associated with suicidal thinking and attempts in combat Veterans. Specifically, transgressions by self (e.g., acting in ways that violated one's moral code or values) were associated with elevated odds of suicidal thinking, and feelings of having been betrayed by the military (e.g., feeling betrayed by fellow service members that one once trusted) were associated with a 2-fold greater likelihood of attempting suicide. These results underscore the importance of moral injury in suicide risk models and of assessing and treating moral injury in Veterans at risk for suicide.

Using the NHRVS data, investigators also examined factors that protect against the development of suicidal thinking over a 4-year period. Results revealed that 7.5% of Veterans developed suicidal thinking. Greater loneliness, disability in activities of daily living, PTSD symptoms, physical distress, alcohol use problems, and denial-based coping increased the likelihood of developing suicidal thinking. Protective factors associated with decreased likelihood of suicidal thinking included greater social support, curiosity, resilience, and acceptance-based coping.

Other work using NHRVS data observed that alcohol use disorder (AUD) and a history of homelessness increased suicide attempts in Veterans diagnosed with PTSD. Veterans with comorbid PTSD and AUD were more than 3 times as likely as Veterans with PTSD alone to have attempted suicide in their lifetimes.

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

Division researchers are currently conducting: 1) a clinical trial of repeated doses of ketamine for treatment-resistant PTSD, with an added emphasis on durability of treatment response; 2) validation of a new type of treatment for PTSD using neurofeedback to specifically target activity of the amygdala, a brain region that has been found to be hyperactive in PTSD; 3) a 7-day trial of PE enhanced with a single infusion of ketamine; 4) a project examining the effectiveness of Mindfulness Based Stress Reduction for anger and aggression in Veterans with PTSD, 5) a trial of transcranial direct current stimulation on learning, memory, and brain circuitry and 6) a trial of buprenorphine and CPT for patients diagnosed with PTSD and opiate use disorder.

Finally, using data from VA Cooperative Studies Program (CSP) Study #504, which evaluated the efficacy of risperidone for chronic, antidepressant-resistant, military service-related PTSD, investigators evaluated correlates of treatment non-response. Greater severity of PTSD symptoms, particularly re-experiencing (i.e., nightmares) and emotional numbing

(Clinical Neurosciences Division, continued)

(i.e., sense of foreshortened future), was associated with non-improvement to both placebo and risperidone over the 24-week trial.

**DSM-5**

Data from the NHRVS revealed lifetime and past-month PTSD prevalence rates of 8.1% and 4.7%, respectively, with the likelihood of developing PTSD (28.0%) highest for Veterans who experienced sexual abuse during childhood. Investigators also found that 19.2% of Veterans with lifetime PTSD and 16.1% of Veterans with past-month PTSD screened positive for the dissociative subtype. Other work examined prevalence and comorbidities associated with subthreshold PTSD, finding that 22.1% and 13.5% of Veterans screened positive for lifetime and past-month subthreshold PTSD, respectively. Subthreshold PTSD was associated with substantially elevated rates of major depression and suicidal thinking, as well as reduced mental and physical functioning. Other work comparing the prevalence of PTSD according to *DSM-5* and International Classification of Diseases 11<sup>th</sup> revision (ICD-11) criteria indicated higher prevalence of lifetime and past-month PTSD using *DSM-5* relative to ICD-11 criteria, suggesting that ICD-11 criteria may fail to identify a

considerable proportion of Veterans with clinically significant PTSD symptoms, thus affecting eligibility for health care, disability, and other services.

Finally, following a dimensional and structural evaluation of *DSM-5* PTSD symptoms, investigators proposed a novel, 7-factor hybrid model of PTSD symptoms that includes: 1) intrusions, 2) avoidance, 3) negative affect, 4) anhedonia, 5) externalizing behaviors, 6) dysphoric arousal (e.g., sleep difficulties), and 7) anxious arousal (e.g., hypervigilance) symptom clusters. This model has been replicated in more than a dozen other trauma-affected populations worldwide. Further studies evaluated the nature and stability of the network structure of *DSM-5* PTSD symptoms using state-of-the-art network modeling approaches. Results of these studies revealed that negative trauma-related emotions, flashbacks, detachment, and physiological reactivity to trauma cues were central symptoms of the disorder and may contribute to its chronicity. They further indicated that self-destructive behaviors associated with trauma were strongly related to suicidal thinking, thus highlighting the importance of trauma-related externalizing behaviors in predicting suicide risk in Veterans.

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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 treatments that employ the potential benefits of technology-based delivery of services.

**PTSD and Suicide**

Staff are developing participatory system dynamics modeling tools that clinic teams can use optimize allocate of 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.

**Treatment Efficiency, Effectiveness, and Engagement**

Several projects are aimed at increasing patient engagement into care, improving access to care and using technology to increase the reach, efficiency and effectiveness of treatment. One study is developing a brief measure of patient characteristics associated with effective engagement in care. The measure is expected to guide identification of the type and amount of service resources needed to engage Veterans into care. A second study will focus 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 risk-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 benefits of web-based and app-based technologies to increase Veteran access to mental health care and to enhance outcomes. Telemental health services to the home are expected to increase patient engagement and access to care, but this type of service is rarely implemented to date. 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. The goals of the study are to assess the relative effectiveness of these treatments and to identify barriers and facilitators for using video to home delivery treatment. The efficacy of a web version of Prolonged Exposure (PE), entitled web-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 VA-funded 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 Therapy, with and without peer support.

### (Dissemination and Training Division, continued)

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 service. Several pilot studies of mobile phone apps are near to 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 and PTSD will determine the efficacy of a novel neurocognitive intervention for improving recovery outcomes.

In collaboration with investigators from the Minneapolis VA, the Dissemination and Training 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 another highly stressed population: cancer survivors.

#### **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 data emerging from the project indicate substantially reduced wait times for treatment enrollment at facilities using this method compared to those using routine enrollment strategies. Additional funding has been obtained to assess the cost-effectiveness of this approach and to test its mechanisms of action.

A trial testing whether a curated online information resource can increase VA, Department of Defense (DoD), and community providers' knowledge about core elements of the [VA/DoD Clinical Practice Guideline for PTSD](#) is ongoing. Analyses are still underway, but initial results suggest that the intervention increased clinicians' familiarity with some key practices. A long-term project is the development of a

practitioner network across both VA and DoD that can test strategies for implementing best practices. The network is currently engaged in quality-improvement projects, but can become a resource for implementation science research in the future.

#### **Implementation**

A new study is evaluating how to simplify assessment of the quality of delivery of cognitive-behavioral therapy (CBT) for PTSD, depression, and anxiety disorders. 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 investigating the effectiveness of different training models on trainee delivery of PE. Another study compares methods of assessing treatment quality and fidelity (important implementation outcomes) for CBTs, including CPT.

In collaboration with the Minneapolis VA, investigators at two National Center Divisions are testing an implementation toolkit and facilitation to increase use EBPs in VA PTSD clinics. This project leverages findings from a prior study on organizational factors that contribute to wider use of EBPs. A new multisite trial will test whether a tailored set of implementation strategies increases the use of PE within the military health system above and beyond the impact of standard provider training. This mixed-methods study will engage stakeholders at various levels and then match implementation strategies to site-specific barriers and facilitators. National Center staff are also supporting and helping to evaluate VA's efforts to implement measurement-based care (MBC).

#### **Other Important Research**

A database is in the process of being developed to house and organize national patient level data regarding PTSD assessment and treatment characteristics. This "at-your-fingertips" database will provide specific and critical information about VA delivery of PTSD care that will quickly orient researchers about important gaps in knowledge and critical next questions to investigate regarding PTSD care.

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## Evaluation Division

The Evaluation Division in West Haven, Connecticut, supports the National Center's mission through a programmatic link with the 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 NEPEC is primarily engaged in evaluation research, is also works on independent research projects related to the treatment of PTSD.

(Evaluation Division, continued)

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

NEPEC has continued to monitor and assess PTSD treatment at VA. The monitoring includes both residential and outpatient specialty treatment programs, as well as PTSD treatment by trained providers not working within one of the PTSD specialty programs. The Evaluation Division via NEPEC also monitors efforts to improve psychotropic medication prescribing practices at the Veterans Health Administration (VHA). Two of the measures in this initiative are the use of antipsychotics to treat PTSD and the use of benzodiazepines without an appropriate diagnosis or medical indication.

The Clay Hunt Suicide Prevention Act of 2016 required that VA employ an outside independent evaluator to determine the effectiveness, cost effectiveness and satisfaction with VA mental health programs. Evaluation Division staff served as the primary liaison to the Clay Hunt evaluation team, providing data, methodological consultation and contextual interpretation for findings of the evaluation studies. The first annual report of these findings concluded that both outpatient specialized PTSD care and residential PTSD services are effective at reducing symptoms and improving functioning in the first 90 days of treatment, are cost effective, and that Veterans are largely satisfied with services. The evaluation studies will continue annually, with a more in-depth look at the role of concurrent mental health treatment and comorbidity a focus of evaluation in the coming year.

The Evaluation Division continues research on PTSD health services research, pain management, and the role of pain in the treatment of PTSD, as well as on sex differences in the health of returning Veterans. Data collection for a study of the implementation of two EBPs—PE and CPT—in 38 VA residential treatment programs (RTPs) for PTSD has been completed. Findings continue to be published on provider perspectives on perceived effective residential treatment ingredients, provider perceptions of dissuading factors to the use of PE and CPT, and changes in implementation of PE and CPT over time.

The Evaluation Division has a number of investigators using administrative data to explore treatment patterns and outcomes of PTSD care. Studies of medication use for the treatment of PTSD, as well as on correlates of self-reported PTSD symptom severity scores over time, have been published. During FY 2019, the Evaluation Division will further examine the role of pain in specialized PTSD treatment and in the treatment of comorbid PTSD and pain, and will continue publishing results from the Survey of Returning Veterans (SERV) interviews.

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

The MBC in Mental Health Initiative, which was formally launched by OMHSP in June 2016, completed its second year

of work. As part of Phase II of the Initiative, every intensive substance abuse outpatient program and every RTP was required to implement MBC. Two Evaluation Division staff are supporting the initial pilot program evaluation; members of the Executive Division and the Dissemination and Training Division are involved in the senior leadership of the Initiative. Additional investigators from within the Center are closely involved in the evaluation study itself, as well as in the Communications, Education and Training, and Coaching work groups. The National Center investigators from the Dissemination and Training Division secured a contract with the RAND Corporation to perform in-depth interviews with MBC project directors, frontline provider-Veteran dyads, and individual providers to better understand their experiences with MBC, and those data have been collected and are currently being analyzed. As the Initiative moves into its third year, NCPTSD members will continue to be active participants as investigators and as Initiative leaders.

The national Psychotropic Drug Safety Initiative has entered its fifth year and has been tracking data on changes in practice in prescribing for PTSD, seeing a continued drop in the use of benzodiazepines among Veterans with PTSD. The Evaluation Division continues its work with technical advisors at the PTSD Mentoring Program and at the OMHSP to provide technical assistance to this Initiative. The Division also continues to respond to requests from specialized programs and staff in the field on policy, operations, handbook implementation, and the provision of evidence-based practices.

### **Other Important Research**

Recruitment has finished for the SERV study, which is a repeated panel study of gender differences in psychiatric status and functioning among Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn Veterans. SERV recruited 850 participants who were interviewed at three-month intervals for at least a year; a sizeable subset continued interviewing for up to three years. Over 40% of the sample is women. Follow-up rates are 80% - 85%. Analyses in a number of areas have been undertaken, with seven manuscripts published, in press or under review. The Evaluation Division is looking for investigators interested in analyzing the SERV data, or in leveraging the SERV sample in add-on or other primary data collection studies. Papers have been published on military sexual trauma (MST) and PTSD as they relate to unit cohesion, gender differences in prevalence rates of disorders over time, and characteristics of Veterans endorsing sex addiction items. Other papers and presentations are in progress on insomnia and PTSD symptoms, suicidal ideation and behaviors, and behavioral addictions. SERV data and an add-on study have been used to develop a pornography addiction scale that is currently in testing for psychometric properties; results in international samples are positive.

## Executive Division

The Executive Division in White River Junction, Vermont, provides leadership, directs program planning, and promotes collaboration to facilitate optimal functioning of the other Divisions both individually and collectively. The Executive Division specializes in the development and evaluation of innovative and authoritative educational resources, in programs that disseminate and implement best management and clinical practices, and in the use of technologies to reach a broad range of audiences. The Executive Division also oversees the administration of VA's National PTSD Brain Bank. The Executive Division does not have a specific research mission; investigators are involved in independent and collaborative research in a number of domains such as treatment outcome research, shared decision-making, and biological research.

### Biomarkers

Dr. Matthew Friedman, Senior Advisor to the National Center, continued 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 furthering assessment and treatment techniques. Enrollment of potential postmortem donors began in May 2015 with the launch of the PTSD Brain Bank website. Initially, the Brain Bank was a five-part consortium; it has subsequently grown to seven parts, with facilities at six VA Medical Centers (Miami, Florida; Durham, North Carolina; Boston, Massachusetts; San Antonio, Texas; West Haven, Connecticut; and White River Junction, Vermont) and the Uniformed Services University of the Health Sciences. The Clinical Neurosciences Division is the primary data analysis site; please see the Clinical Neurosciences Division narrative for more information about ongoing research endeavors utilizing PTSD Brain Bank tissue.

As of the end of FY 2018, the Brain Bank had 218 PTSD and comparison frozen hemispheres (roughly divided in thirds from donors with PTSD, donors with major depression, and healthy controls). In addition, the Brain Bank has 22 fixed hemispheres. An additional 90 prospective tissue donors have volunteered to be followed over their lifetimes. The Brain Bank has begun an exciting collaboration with the Lieber Institute for Brain Development that will obtain RNA sequencing and DNA methylation data from ten brain regions from over 300 brains, divided between PTSD, major depressive disorder, and healthy controls.

Executive Division investigators are also involved in biomarkers research utilizing fMRI and EEG. One ongoing project is the first study of the neural correlates of social working memory in PTSD. Investigators are testing whether PTSD is characterized by difficulties maintaining and manipulating social information on a moment-to-moment basis and whether such difficulties are associated with poorer social connection. A separate 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.

### PTSD and Suicide

Executive Division researchers continue to advance the new priority area of PTSD and suicide through collaborations with the National Center for Patient Safety (NCPS), OMHSP, and the Center of Excellence for Prevention of Suicide (COE). Pilot work sponsored by NCPS has led to the development of two large-data oriented grant proposals to VA and DoD, the most recent of which seeks to evaluate the effect of evidence-based PTSD treatments on reduction in death by suicide. An ongoing collaboration with OMHSP validated a prior finding about high-risk periods for suicide following psychiatric discharge. These findings have supported current pilot work in high-risk populations at the White River Junction VA. Ongoing work with the COE evaluates potential misclassification in suicide outcomes. Finally, a separate study is using semantic analysis of clinical note text to evaluate ruptures in therapeutic alliance preceding death by suicide in a VA PTSD treatment population.

### Treatment Efficiency, Effectiveness, and Engagement

The Executive Division has a long history of participation in VA's CSP. During FY 2018, enrollment for 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. Data collection is projected to end in the 2<sup>nd</sup> quarter of FY 2019. 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 for PTSD previously developed [AboutFace](#), a public awareness campaign to help Veterans recognize PTSD and motivate them to seek best practice treatment. In FY 2018, investigators launched a project in which they will examine the impact of AboutFace on engagement in and completion of evidence-based treatment among Veterans with PTSD. 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. Data collection for a trial comparing two psychotherapies for comorbid AUD and PTSD (PE and Seeking Safety) was completed in December 2017. Primary outcome analyses are underway. Recruitment for a trial that is evaluating the combination of topiramate and PE for co-



### (Executive Division, continued)

occurring PTSD and AUD is ongoing. Investigators continue collaborations with the PTSD specialty clinics and with the residential PTSD/substance use treatment program at the San Diego VA to develop ways to use clinical data for research. An ongoing pilot study is investigating the safety and efficacy of a novel form of synchronized transcranial magnetic stimulation for PTSD with comorbid depression; results are expected in FY 2019. The first study of cannabidiol-enhanced PE in Veterans was funded in FY 2018 and will launch in FY 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 is midway through recruitment.

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

The Executive Division is working on several initiatives aimed at assessing models of care and at improving evidence-based practice. Investigators continue to analyze data and publish results from a national survey that assessed the treatment needs and preferences of Veterans and non-Veterans with PTSD symptoms. Results of this survey informed the development of the first publicly available online treatment decision aid for PTSD, which was released to the National Center website in March 2017. The [PTSD Treatment Decision Aid](#) is interactive and enables users to identify preferences among treatment options and print that information to share with their provider. Current work focuses on evaluating patient preferences for evidence-based PTSD treatments and investigating how different methods of presenting treatment information can impact these preferences.

Executive Division investigators continue to examine the impact of facilitation and an academic detailing intervention, in which a pharmacist and psychologist reach out directly to VA clinicians in rural clinics, to improve PTSD treatment practices throughout VA New England Healthcare System. In a new initiative, investigators expanded their intervention

to rural facilities outside of New England to share guideline-recommended practices for PTSD. Special emphasis was placed on unique methods to reduce benzodiazepine prescribing through a Direct-to-Consumer educational outreach approach. Additionally, innovative natural language processing methods are being used to identify rural sites across the country that are low in delivery of EBPs.

In addition to projects aimed at improving clinical practices, investigators are continuing to assess the state of VA care for PTSD. Ongoing work applies novel informatics and operational methods to medical and administrative data in order to understand multiple dimensions of quality of PTSD care within VA. In FY 2018, investigators determined the longitudinal use of EBP and evidence-based antidepressants (EBAs; fluoxetine, sertraline, paroxetine, and venlafaxine) over the 10-year period of observation. With regards to uptake of EBPs, there was a steady increase in the use of PE and CPT over the 10-year period but little change in the use of EBAs. Planned projects include development of quality standards for EBP and EBA receipt that are reflective of improvement in PTSD symptoms, and to use these standards to establish predictors of the receipt of effective and timely PTSD treatment.

#### **DSM-5**

In collaboration with the Behavioral Science Division, the Executive Division is leading a study 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 collection will be completed by the end of FY 2018.

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## 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 dissemination phase of a large trial that examines 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 that compares different treatments for in-home delivery of a couples-based intervention for PTSD was recently launched;

this study examines the clinical efficacy of Cognitive-Behavioral Conjoint Therapy for PTSD, 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. Lastly, an additional collaboration involves a multi-site trial comparing standard PE with PE incorporating a partner.

(Pacific Islands Division, continued)

### 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 continue 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, Latino, Asian American and 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 1 of the interview examines who in their social networks veterans talk to about mental health 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. Additional projects include collaborations on a national qualitative study examining drop-out from EBPs with investigators from the Women's Health Sciences Division and Minneapolis Health Services Research & Development Center of Innovation, and a project developing a statistical methodology that will allow for estimation of 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

Biomarkers work at the Women's Health Sciences Division includes studies aimed at explaining the basic biological processes underlying PTSD with particular relevance to women: a study examining the role of neurobiological and psychosocial factors that impact negative pregnancy outcomes among women with PTSD; 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 series of studies of the gene-environment interplay in the comorbidity of PTSD and eating disorders; and a study of GABA-ergic neuroprotective steroids in men and in women across the menstrual cycle. Recently published work using plasma measures has demonstrated that women with PTSD are at heightened risk for decreased conversion of progesterone into its anxiolytic metabolites.

Studies investigating the role of biomarkers in intervention efforts include a study investigating whether a specific electrophysiological response pattern to a series of loud tones is predictive of selective serotonin reuptake inhibitor (SSRI) response among men and women, in an effort to identify individuals who are likely to respond to SSRI treatment. The Women's Health Sciences Division is also working on two studies investigating the role of progressive exercise training, to determine whether it affects participants' capacity for releasing shared neurohormones to help reduce or better manage chronic pain (including fibromyalgia) and PTSD symptoms.

### PTSD and Suicide

Ongoing work in the area of suicide includes a large-scale epidemiologic machine learning study of suicide. Specifically, using data from the entire population of Denmark from 1995-2015 investigators are applying machine learning techniques to develop prediction models for suicide attempt and death from suicide. Analyses will be conducted on the full population, as well as among subgroups including all of those diagnosed with PTSD and women diagnosed with PTSD.

### Treatment Efficiency, Effectiveness and Engagement

Recent efforts focused on treatment engagement identified that Veterans who were unwilling to engage in PTSD or depression treatment were willing to seek treatment for sleep difficulties, suggesting this may be an important gateway to engaging some Veterans into treatment. Other work has examined treatment engagement of subpopulations of interest, including an examination of PTSD treatment seeking experiences in a sample of discrimination-based trauma-exposed lesbian, gay, bisexual, and transgender Veterans.

Several intervention studies are examining more efficient treatment formats for CPT. With support from the [South Texas Research Organizational Network Guiding Studies on Trauma and Resilience \(STRONG STAR\)](#) Consortium, investigators are continuing to analyze data from a recently completed 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

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

treatment end is determined by patient progress. Another trial will test the efficacy of CPT delivered in an intensive outpatient format with active-duty military Servicemembers.

In terms of treatment effectiveness, investigators are working to improve adherence to existing PTSD treatments. A current study is exploring Veteran and provider perspectives on reasons for dropout from both CPT and PE to develop an intervention aimed at increasing rates of completion for these treatments.

Other intervention studies focused 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. Another ongoing intervention examines the effectiveness and fit of a transdiagnostic treatment, the Unified Protocol, for trauma-exposed Veterans with co-occurring diagnoses.

The Women's Health Sciences Division is also focused on intervention research among those who have not necessarily been diagnosed with PTSD, including examination of the effectiveness of a national network of peer-facilitated psychoeducation and support groups for women Veterans who want to improve their well-being, titled [WoVeN: The Women Veterans Network](#).

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

The Division's focus on care delivery within VHA emphasizes care for conditions with particular relevance to women Veterans. These include a mixed-methods investigation of Veterans' experiences with and preferences for VHA's universal MST screening program. Two additional 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, generally and specific to eating disorders.

Additional work has 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. Recent analyses highlight several key differences between the post-military readjustment of male and female Veterans, including female Veterans' greater likelihood of experiencing mental health concerns and seeking health care within the first year after separation.

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 current analyses is the relationship between Veterans' functioning and their service use, with findings suggesting that functional impairments may serve as a facilitator of treatment seeking for women whereas it may impede treatment seeking for men.

#### **Implementation**

Investigators within the Women's Health Sciences Division are conducting implementation research focused on identifying and disseminating best practices for intimate partner violence (IPV) identification, assessment, treatment, and the targeting of health services within the VHA context. In terms of screening, investigators conducted a national qualitative evaluation of early and late adopting VA Medical Centers to identify best clinical practices for IPV screening and response practices, as well as successful implementation strategies to be used to scale-up these practices throughout VA primary care. A complementary study evaluated the reach, adoption, and effectiveness of a risk assessment screening tool for women who experience IPV and found that implementation of the tool is associated with increased access to psychosocial services. These findings are being adopted within VHA in a planned randomized program evaluation to assess the implementation impact and effectiveness of IPV screening programs.

In terms of implementation of interventions associated with IPV, investigators 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.

#### **Other Important Research**

Within the Women's Health Sciences Division, research beyond these key operational priorities generally focuses on investigations of key, understudied gender differences or better characterizing the experiences and health burden experienced by women who have been exposed to trauma. As part of improving the understanding gender differences in stress, trauma, and related psychiatric outcomes, the Longitudinal Investigation of Gender, Health, and Trauma study is a national survey of Veterans, focusing on more clearly delineating the impact of trauma and community violence on mental, physical, and reproductive health among both women and men.

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

## Appendix B: Fiscal Year 2018 Research Narrative

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

strategies. Investigators will be able to examine sex differences across domains of measurement by comparing this sample with comparable male samples.

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, on later life health, functioning, and disability in Vietnam-era women Veterans. In collaboration with investigators in the Behavioral Science Division, a follow-up study of female and male Vietnam-era Veterans is examining predictors of mortality, as well as changes in physical and mental health-related well-being over time.