



The VA Parkinson Report

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A Newsletter for the Parkinson's Disease Research, Education and Clinical Centers
and The National VA Parkinson's Disease Consortium



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Phase Transition: A New Phenomenon in Parkinsonian Disorders

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The past decade has seen an explosion in our understanding of proteins and genes underlying neurological diseases. No longer do amyloid-beta, tau, and alpha-synuclein alone draw experts' attention. Newer players on the scene include TAR DNA-binding protein (TDP)-43, fused in sarcoma (FUS), and a number of other proteins that play a role in sporadic and inherited neurological disorders.

While it is convenient to consider amyloid-beta, for example, as the "Alzheimer's protein," or alpha-synuclein as the "Parkinson's protein," it now appears that neurodegenerative proteins may work together to cause an overlapping array of conditions. This theme of overlapping sets of symptoms arising from a single cause was highlighted by the discovery in the late nineties of patients with mutations in tau with varying combinations of frontotemporal dementia, parkinsonism, and motoneuron disease. Subsequently, mutations in valosin-containing protein (VCP) were identified as a cause of inclusion body myopathy with frontotemporal dementia and bone disease; this and a group of related disorders are now referred to as multisystem proteinopathies (MSP). Many MSP proteins, as well as TDP-43 and FUS, are RNA binding proteins and contain regions of low amino acid complexity that have a tendency to self-associate.

In classical cell biology, structures that carry out the business of the cell (organelles) are bounded by membranes. It has become clear more recently, however, that structures such as RNA granules are liquid droplets without membranes. Recent studies have shown that the tendencies of proteins such as TDP-43 and FUS to self-associate can lead to phase transition from mixed liquid-solid to liquid phase droplets. This process is something like the separation of well mixed oil and vinegar in a salad dressing to separate liquid and oil phases.

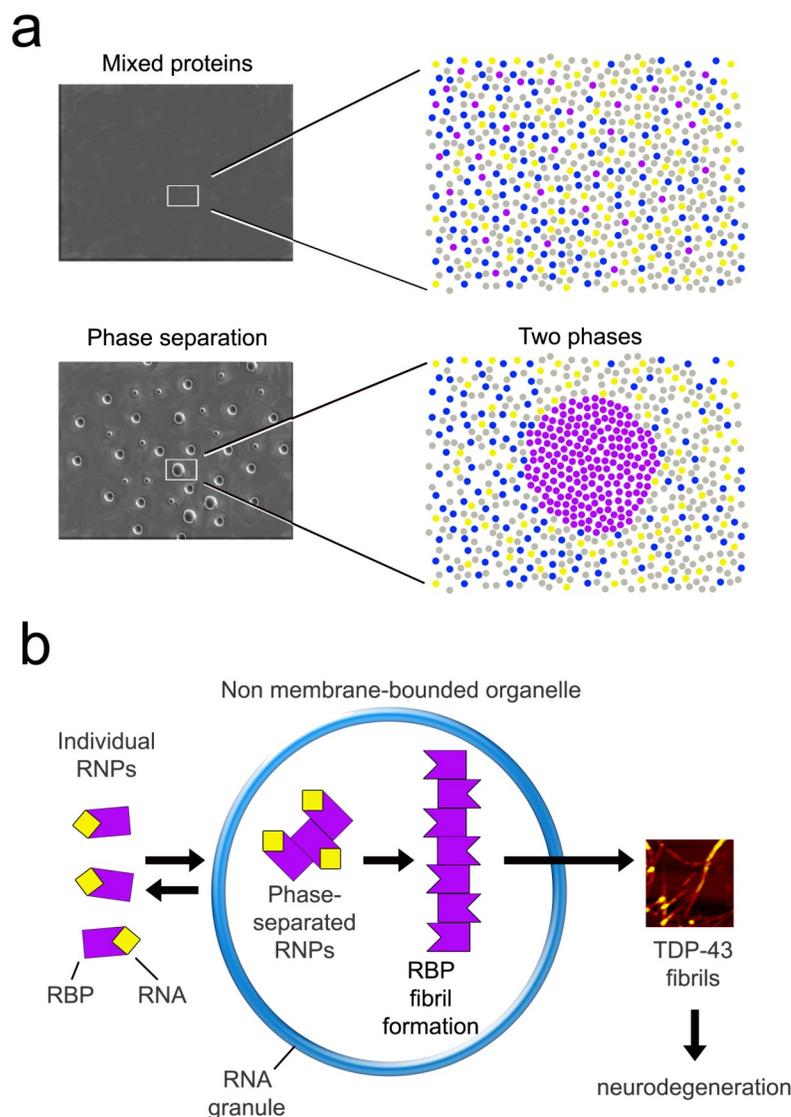
Figure 1 shows a schematic explaining a possible relationship between phase separation and aggregation of TDP-43 into neurotoxic aggregated protein fibrils. In panel A, a mixture of RNA-binding proteins with self-association domains can transition from a mixed phase (upper panel) to two separate phases (lower panel), one of which is a liquid droplet (magenta). Panel B shows a mixture of ribonucleoproteins, each containing both RNA (yellow) and RNA-binding proteins (RBP; magenta). These can undergo phase separation to form droplets, such as RNA granules. In this environment, self-association of the RBP favors aggregation, which contributes to the formation of toxic fibrils that cause neurodegeneration.

Phase Transition: A New Phenomenon in Parkinsonian Disorders (continued)

The equilibrium between mixed phases and fibril-promoting phase separation may present a novel therapeutic target. In the lab, certain chemicals can disperse liquid droplets such as these, much as a crafty cook can use egg yolk to create a mixed oil and liquid emulsion for a salad dressing. This might lessen the tendency of RNA binding proteins to aggregate and form toxic fibrils.

How important are phase separations to persons with Parkinson's and the PADDRECC? While it is true that some FUS mutations appear to cause essential tremor or atypical parkinsonism, most of the related proteins are more closely associated with frontotemporal dementia and motoneuron disease/amyotrophic lateral sclerosis (ALS). At a recent conference in Belgium, however, data were presented suggesting that tau also may undergo toxic phase separation, despite having self-association domains that are different from those in TDP-43 and FUS. As tau aggregation is associated with both Alzheimer disease and the Parkinson plus disorder, progressive supranuclear palsy (PSP), it seems likely that understanding of phase separation will be important in developing effective treatments for Parkinson disease and related disorders.

Figure 1. Schematic of the proposed relationship between phase separation, aggregation, and fibrillization of an RNA-binding protein such as TDP-43. Adapted and simplified from Taylor, Brown, and Cleveland, 2016.



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Investigation of the Causes of Parkinson's Disease, Particularly Factors Affecting Veterans

Caroline M. Tanner, MD, PhD, Director, San Francisco PADRECC

Veterans may be at risk for Parkinson's Disease (PD) due to service related exposures. Environmental factors associated with greater risk of PD include pesticides, solvents, traumatic brain injury (TBI), among others^{1,2} Exposure to many of these risk factors may occur during military service.

Pesticides: An association between pesticide exposure and PD has been confirmed, based on more than 80 populations studied, and the Movement Disorders Society research criteria for assessing probability of prodromal PD include pesticide exposure.³⁻⁵ Several pesticides are particularly relevant to Veterans.

a) 2,4-dichlorophenoxyacetic acid (2,4-D) was associated with double the risk of PD in a civilian population.⁶ 2,4-D is a component of Agent Orange, a tactical herbicide mixture used extensively in Vietnam and a presumptive cause for PD in Veterans.⁷

b) Permethrin: Occupational exposure to permethrin, an insecticide that blocks mitochondrial Complex I and causes oxidative stress, tripled the risk of PD in one study⁶, but the effect was less marked in another.⁸ Military use of permethrin- or lindane-permeated uniforms is common, and permethrin can be dermally absorbed.^{9,10}

c) Organophosphate insecticides are commonly used to control insect disease vectors. Exposure to methyl parathion⁸ and chlorpyrifos¹¹ may be associated with increased PD risk. Military exposure to cholinesterase inhibitor pesticides and concurrent prophylaxis with pyridostigmine has been proposed to contribute to the syndrome of neurological and somatic symptoms constituting the Gulf War Syndrome.^{10,12,13}

d) Paraquat: Pesticides are also used on bases or in combat settings to control plant overgrowth. Paraquat (1,1'-dimethyl-4,4'-bipyridinium dichloride), among the most common, can increase production of reactive oxygen species, alpha-synuclein aggregation and cause selective nigral injury.¹⁴⁻¹⁷ PD risk more than doubled with occupational paraquat use, and risk increased in those residing near treated fields.^{3,6,8,18,19}

Traumatic Brain Injury (TBI): Mild to moderate head injury, typically occurring decades before PD onset, has been associated with greater risk of PD in many studies.²⁰⁻²⁴ TBI can disrupt the blood brain barrier, increasing CNS passage of toxicants, and triggering inflammatory processes that interfere with axonal transport and induce aggregation of alpha-synuclein and tau—processes that may ultimately lead to neurodegenerative changes.²⁵

TBIs commonly occur during military service as the result of blast injuries, vehicle crashes, falls or other injuries. An estimated 285,000 Iraq and Afghanistan Veterans have been diagnosed with TBI as of 2008. The VA has published a new regulation, providing for the consideration of PD and certain dementing disorders as service related disabilities in Veterans with moderate to severe service-related TBI.²⁶

Chlorinated Solvents: Occupational exposure to chlorinated solvents is associated with an increased risk of PD.^{27,28} In World War II Veteran twins, PD risk was increased 6 fold after trichloroethylene (TCE) use, and greater risk was suggested for perchlorethylene (PERC, OR: 10.5, 95% CI: 0.97-113), and carbon tetrachloride (OR: 2.3, 95% CI: 0.9-6.1).²⁸ TCE causes experimental parkinsonism in rats, producing reactive microglia, mitochondrial Complex I inhibition, oxidative stress, alpha-synuclein aggregation and degeneration of dopaminergic neurons. Chlorinated solvents are commonly used as cleaners and degreasers in military and civilian settings.²⁹ They are environmentally persistent, and non-occupational exposure may occur.

Camp Lejeune: For example, levels of PERC and TCE were up to 3000-fold greater than EPA permissible levels in residential drinking water systems at Camp Lejeune, NC, between 1953 and 1987. Based on guidance from the Institute of Medicine advisory panel,³⁰ the VA recently designated PD as a presumptive service-connected condition for the approximately **1million** Veterans who lived at Camp Lejeune during this 35 year period³¹.

Prisoner of war status has been associated with increased PD risk^{32,33}, but this is controversial.³⁴ Extreme physical and psychological stress increase dopamine turnover and enhance oxidative stress. Our preliminary analysis of VA data also finds an increased risk of PD in former POWs.

Investigation of the Causes of Parkinson's Disease, Particularly Factors Affecting Veterans (continued)**References**

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Investigation of the Causes of Parkinson's Disease, Particularly Factors Affecting Veterans (continued)

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Philadelphia Researchers Recognized for Innovative Bioengineering Approach to Parkinson's Disease Treatment

John Duda, MD, Director, Philadelphia PADRECC

The Center for Neurotrauma, Neurodegeneration, and Restoration (CNNR) at the Corporal Michael J. Crescenz VA Medical Center in Philadelphia was established in 2015 under the Co-Direction of Dr. Kacy Cullen and Dr. John Duda, who also serves as the Director of the Philadelphia PADRECC. The CNNR was designed to bring together researchers in the fields of neurology, neurosurgery, rehabilitation and bioengineering as a comprehensive research hub building on strengths in neurotrauma, neurodegeneration, and restorative tissue engineering to improve the long-term health of our Veterans. At present, the CNNR has 9 active VA-approved studies across CNNR faculty; \$3,046,000 in total annual direct costs across CNNR faculty (\$933,000 of which is VA funding); and total funding of over \$13 million through 2021 (over \$4 million from VA).



From left to right: Dr. Duda, Kevin Browne, Laura Struzyna & Dr. Cullen

The center's research aims are widespread and range from attempting to model chronic traumatic encephalopathy in animals to cellular replacement strategies for Parkinson's disease. In order to address some of the limitations of traditional cell based replacement strategies, Dr. Cullen and his colleagues have developed micro-tissue engineered neural networks (micro-TENNs) designed to repair or replace damaged regions of the brain or nervous system. Although loss of neuronal connections (axons) is a prominent feature of many neurological diseases and trauma, there was no strategy capable of repairing long-distance axonal connections in the brain. Dr. Cullen's team has developed techniques to generate neurons with long axonal tracts encased in miniature hydrogel tubes and are using these micro-TENNs as a strategy to facilitate nervous system repair by directly replacing circuitry in the brain. In a study funded by the Michael J. Fox Foundation, CNNR researchers have been studying the feasibility of using micro-TENNs to treat Parkinson's disease by replacing the nigrostriatal pathway, which connects the dopaminergic neurons of the substantia nigra to their target, the striatum.

Laura Struzyna, a 5th year graduate student in the lab, is currently examining the *in vitro* characterization of micro-TENNS, their ability to release dopamine and whether replacing the nigrostriatal pathway with engineered dopaminergic micro-TENNs can reverse motor symptoms in animal models of Parkinson's disease. She has been able to construct micro-TENNs the width of a human hair, consisting of an exterior hydrogel shell surrounding an interior extracellular matrix that supports robust neuronal axon growth approximately ten times longer than previously reported. She has proven the micro-TENNs are functional by showing that when electrically stimulated, the micro-TENNs release dopamine. Finally, the research team has been able to successfully implant the micro-TENNs into the rat brain, recapitulating the nigrostriatal pathway. The micro-TENNs constructs have shown signs of integration with host tissue and researchers are currently assessing behavioral outcomes.

These studies were recently presented in abstract form at annual meeting of the International Congress of Parkinson's Disease and Movement Disorders in Vancouver, Canada and honored by inclusion in the Blue Ribbon Highlight Session as well as in the American Academy of Neurology's *Neurology Today* Conference Report dated June 13, 2017 (<http://journals.lww.com/neurotodayonline/Pages/International-Congress-of-Parkinsons-Disease-and-Movement-Disorders.aspx>).

The micro-TENN approach is the first that fully reconstructs the degenerated pathway that produces many of the motor symptoms in Parkinson's disease. If successful, this strategy, developed by VA researchers, has the potential to provide symptomatic relief for people with Parkinson's disease, Veterans and non-Veterans alike.

Philadelphia PADRECC Update

Education News

Monthly Video Case Conference

Monthly video case conference calls are held with service area Consortium Centers to share case studies and discuss diagnosis and treatment of difficult cases.

National VA Parkinson's Disease Consortium Conference

The Philadelphia PADRECC led the planning and execution of the 2016 conference which was held in Portland, Oregon prior to the World Parkinson's Congress. The following PADRECC physicians presented at the conference: Dr. John Duda: "Nutritional Considerations in PD," Dr. James Morley: "Drug-Induced Parkinsonism," and Dr. Daniel Weintraub: "Management of Psychiatric Complications of PD."

2016 World Parkinson Congress

The National VA PD Consortium was an Organizational Partner of the 4th World Parkinson Congress which was held in Portland, Oregon. Dr. John Duda and Dr. Daniel Weintraub of the Philadelphia PADRECC were panelists, co-chairs or co-moderators for several sessions of the Congress. The PADRECCs hosted an exhibitor table which provided Congress attendees with information on the PADRECC and National VA PD Consortium programs and services available.

PADRECC/EES Movement Disorders Series

The Philadelphia PADRECC continues to participate in this professional education audioconference held bi-monthly. Dr. James Morley recently presented "Exercise As Medicine." This presentation provided clinicians with information on the current evidence for exercise as a disease-modifying therapy in PD and related disorders. The talk also reviewed evidence about whether exercise may benefit not only symptoms but also influence underlying disease progression. Finally, Dr. Morley discussed the practical aspects of "prescribing" exercise to patients with PD.

10th PADRECC/MIRECC Symposium on Neurodegenerative Diseases: Preclinical and Prodromal Stages of Neurodegenerative and Neurodevelopmental Disorders

The Philadelphia PADRECC in collaboration with the Philadelphia MIRECC hosted this CME program to continue the practice of delivering an informative symposium for clinicians and clinical researchers. With the development and testing of disease-modifying therapies, as opposed to purely symptomatic therapies, the need to identify patients with neurodegenerative diseases as early as possible becomes increasingly important, as early identification and treatment with such therapies has the potential to prevent or delay onset of these diseases (such as Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies, frontotemporal dementia, and schizophrenia). This symposium focused on cutting edge, ongoing research to identify patients at risk (pre-clinical) or manifesting early signs of disease (prodromal). The results of these research studies have the potential to dramatically alter how clinicians screen and manage patients in the general population at increased risk for these disease.

Patient & Caregiver Support Group Program

This program runs from April-December and meets once a month for one hour to provide support and education on topics related to Parkinson's Disease. To increase accessibility, some groups are broadcasted to two local CBOCs using tele-health technology.

Exercise As Medicine-Patient Education Program

This program was held on April 24, 2017 to educate attendees about the benefits of exercise in treating PD. In a 3 hour program, participants were provided with practical information on the benefits of exercise as well as an opportunity to try out different types of exercises shown to be beneficial to the PD population such as Tai Chi, Yoga, Rock Steady Boxing and LSVT BIG. It was a fun morning that got participants moving and realizing exercise can be enjoyable as well as beneficial.

West Haven PD Consortium Site News- Director: Diana Richardson, MD

The West Haven Parkinson's Disease Consortium remains active in promoting good health, well-being and fitness for our Veteran patients with PD. Currently we in our 9th year of offering an annual **PD Lecture & Support Series**. This

Philadelphia PADRECC Update (continued)

year boxing workshops have been added to a mixed program of Wii Sport Fitness, Dance, Yoga and Music therapy. This spring, an Agent Orange Information Research and Education (AO-IRE) support group was launched and plans are being made to expand this group to VISN wide tele-conferencing or audio conferencing in the fall. Lastly, April's celebration of Parkinson Awareness was marked by several Special events. The **Annual Parkinson Fair** provided opportunity to distribute educational materials and to discuss nutrition, pharmacy, physical and occupational therapy, neurology and speech pathology with specialist in an open format style. The **2017 Parkinson's Disease Symposium** focused on Dysautonomia in Parkinson Disease and included formal lectures from Cardiology, Speech Pathology and Urology. And, there was team representation at the **Parkinson's Unity Walk** held in NYC central Park.

Clinical Update

Brain Wellness Clinic

The Philadelphia PADRECC Brain Wellness Clinic which was developed by Dr. John Duda and Heidi Watson, BSN, RN to provide patients the opportunity to focus in-depth on lifestyle choices that can affect brain wellness. Current brain wellness risks are assessed and explored by looking at different lifestyle factors including sleep, nutrition, exercise, mindfulness/spiritual, cognitive and social interaction. During the visit, a thorough interview, several short written or web-based assessments of patients health status, and lab work (if appropriate) are completed. Clinicians discuss wellness goals important to the patient and together develop an individualized plan with realistic and achievable goals, and provide support to implement them. Patients' progress is followed either in person or through telehealth.

Duopa Therapy

The Philadelphia PADRECC, in partnership with the local VA Gastroenterology department, developed a local standard operating procedure for the initiation of Duopa therapy. Philadelphia was the first VA in the country to start Duopa on site. To date, two Veteran patients have started the treatment at the Philadelphia PADRECC.

Research News

Drug-induced Parkinsonism (DIP): A canary in the coal mine?

DIP associated with dopamine receptor blocking drugs (most often antipsychotics) is the second most common cause of Parkinsonism and can be clinically indistinguishable from PD. In some cases, when symptoms persist after drug withdrawal, DIP may represent "unmasking" of prodromal PD-with the offending drugs acting as a "stress test" for dopaminergic pathways.

We previously reported that olfactory impairment (a non-motor feature that often precedes motor symptoms of PD) was more common in patients with persistent DIP (Morley *et al. Park Rel Dis*, 2015). Dr. Morley received a VISN 4 Pilot Award to study the relationship of DIP to PD using DAT-SPECT, olfactory testing and other biomarkers of PD. As part of that study, we have reviewed DAT-SPECT studies for 33 subjects with suspected DIP. DAT-SPECT was abnormal in 7/33 (21%) of suspected DIP cases. Objective olfactory testing was available for 30 subjects and was concordant with the DAT-SPECT result in 27/30 (Odds Ratio=63, 95% CI 4.8-820). Subjects with abnormal scans also had higher scores on the validated PD Non-Motor Symptom Questionnaire. Additionally, subjects with abnormal scans were, on average, treated with lower dose/potency antipsychotics suggesting that the appearance of Parkinsonism with low-intensity dopamine blockers may raise concern for underlying neurodegeneration. This study was recently published in *Movement Disorders: Clinical Practice* and we are continuing to study the relationship between DIP and underlying PD.

Exercise in PD

Identifying early or prodromal PD that has been "unmasked" by DIP offers opportunities for intervention at the earliest stages of disease. Exercise is known to improve symptoms in PD and some evidence suggests aerobic exercise could influence disease progression. In 2016, Dr. Morley received a VA Rehabilitation R&D service Career Development Award entitled "**Effect of exercise on recovery in drug-induced Parkinsonism and Parkinson disease.**" In this study, subjects with suspected DIP who also have abnormal DAT-SPECT are randomized to exercise (aerobic walking) or no intervention. We are examining the short term effects of exercise using the UPDRS and quantitative gait testing after 8

Philadelphia PADRECC Update (continued)

weeks. A potential disease modifying effect of exercise will be assessed using serial DAT-SPECT and biochemical markers after 52 weeks. We will continue to recruit for this study over the next 3 years and plan to eventually expand this intervention into the wider population of patients with early PD.

If exercise can benefit our PD patients, how can we make sure they are getting enough? Dr. Sneha Mantri, PADRECC fellow, is conducting a study to better understand exercise and activity levels in PD. She is examining PD patients' attitudes and barriers to exercise and comparing them to activity levels using both a self-reported survey and objective monitoring in the community using wearable devices. Dr. Mantri hopes to use this information to identify potential interventions to increase exercise and activity levels in PD patients.

Balance and Parkinson's Disease

Dr. Delaram Safarpour, PADRECC Movement Disorders Fellow, and Dr. James Morley, are studying whether a balance vest, Balance Based Torso Weighting (BBTW), can improve walking and balance in patients with PD and related conditions. The weighted vest has been shown to improve walking and balance in patients with other neurological conditions, but it is unknown whether the vest could help patients with PD. Dr. Safarpour is using a sham-controlled randomized crossover design to test the effect of BBTW on walking as measured by clinical impression and quantitative gait and balance assessments. It is hoped that the BBTW can offer a non-pharmacological approach for improvement of balance and walking in this population of patients.

Traumatic Brain Injury

Dr. John Duda, PADRECC Director, and his colleagues, Drs. Kacy Cullen and John Wolf, from the Department of Neurosurgery at the University of Pennsylvania, continue studies funded by the Rehabilitation Research and Development Service of the Department of Veterans Affairs, to develop animal models of Chronic Traumatic Encephalopathy (CTE) that sometimes develops years later in people such as football players and war fighters who have had traumatic brain injuries. The goal of these studies is to develop models of these changes in the brains of animals so that novel treatments and preventive strategies can be tested. It is hoped that these studies will lead to treatments to prevent the development of these neuro-degenerative diseases in Veterans and others who have suffered head injuries.

Neurorestoration in Parkinson's disease and other causes of Brain Injury

Drs. Cullen, Duda and Wolf were awarded a two-year grant from the Michael J. Fox Foundation for Parkinson's Research to investigate experimental reconstitution of the nigrostriatal pathway (the pathway that degenerates in PD and causes the motor symptoms) in animal models of PD in a grant entitled, '**Restoring the nigrostriatal pathway with living micro-tissue engineered axonal tracts**'. This project involves growing cellular constructs in culture, comprised of dopaminergic neurons and the long axonal projections necessary to recapitulate the nigrostriatal pathway. These constructs will then be transplanted into animals that have had lesions of the nigrostriatal pathway to see if these cells can functionally replace the damaged cells. In addition, Dr. Isaac Chen, who is also from the department of Neurosurgery at the University of Pennsylvania and is mentored by Dr. Duda, was recently awarded a Career Development Award from the Rehabilitation R&D Service to try to grow complete cortical structures in culture and transplant them into animal models. It is hoped the lessons learned from all of these studies will one day lead to breakthroughs in our ability to restore function in Veterans suffering from many disorders that affect the brain.

Bacteria and Parkinson's Disease

Dr. Michelle Fullard and Dr. Duda, in collaboration with Dr. Noam Cohen from the Ear Nose and Throat Department, continue to study how bacteria that colonize our body might contribute to the risk of Parkinson's disease. It has been shown that these bacteria are different in people with Parkinson's disease compared to people without Parkinson's disease. This study is trying to understand if there are genetic reasons why some people have certain types of bacteria in the hopes of developing new therapies in the future.

Southeast/Richmond PADRECC Update

Clinical News

Restoring Movement for Our Heroes and Our Community

This article about Deep Brain Stimulation (DBS) <https://www.mcvfoundation.org/news/stories/restoring-movement-our-heroes-and-our-community> highlights the partnership between McGuire Veterans Affairs Medical Center (VAMC) and Virginia Commonwealth University/Medical College of Virginia (VCU/MCV) in Richmond, VA. It features Dr. Kathryn Holloway, Neurosurgeon and Veteran, Charles F. Bryan Jr. who spoke together at a MCV Foundation meeting in June 2017 about the benefits of VA/VCU collaboration.

Duopa another option to consider for certain candidates in treating Parkinson's disease

Duopa is an old medication (carbidopa and levodopa) delivered in a new way. The drug is an enteral suspension or gel that is administered using a tube called a PEG-J (a percutaneous endoscopic gastrostomy tube extended into the jejunum or small intestine). FDA granted approval for Duopa in 2015; however the treatment has been used in Europe for over 10 years under the name Duodopa. Duopa may be an option for those with advanced PD who are experiencing motor fluctuations, more "off" time, more periods of slowness, poor mobility, or irregular response to medication. The Duopa delivery system is designed intentionally to bypass the stomach. Some PD patients with gastroparesis or slow stomach emptying may experience unpredictable absorption of traditional oral medication resulting in poor response/less than optimal symptom control. Duopa hopes to solve this issue with continuous delivery of the medication into the small intestine for 16 waking hours of the day.

Duopa therapy may be appealing for certain patients who have advanced disease process. It may also be suitable for those who might benefit from DBS, but are not a candidate or do not want brain surgery. The decision to start treatment with Duopa should not be taken lightly however. There is a learning curve with multiple steps and several logistics to work through for the patient, care partner, and health care team. The therapy requires surgical placement of a tube, daily hygiene to prevent infection, learning to wear and operate the pump device, changing medication cassettes each day, and working closely with a knowledgeable provider to achieve optimal dosing and symptom management. For a handful of Veterans and their family caregivers, Duopa has been a workable option and helps to smooth out symptoms during the day with less "off" time. As of June 2017, there are two Veterans in the Richmond PADRECC using this therapy, with a few more taking it under consideration. The PADRECC staff works with Gastrointestinal (GI) specialists to arrange PEG-J tube placement and obtain proper tubing through the supply system, pharmacy for the medication, and AbbVie Pharmaceuticals to obtain the pump and garment for patient to wear to contain the pump. Education and informed consent is vital throughout each step of the process, from contemplation, to starting therapy, to ongoing maintenance, and managing disease progression. Duopa is available from the VA pharmacy but through a specialty pharmacy.

Designated Speech Therapist for PADRECC Richmond

Tara Boyle, MS, CCC-SLP is an outpatient speech and language pathologist (SLP) in the Physical Medicine and Rehabilitation (PM&R) Department at McGuire VAMC. Through a collaborative endeavor with PM&R, Tara has established a closer relationship with the Richmond PADRECC team. She is the primary therapist consulted to assist movement disorder patients that need evaluation and therapy for speech and swallowing issues. Tara is certified in LSVT LOUD which she uses along with other techniques when treating patients. She made a presentation to the PADRECC support group about how a speech and language pathologist can help with cognitive issues as well as speech and swallowing. Tara developed a simple self-assessment tool for patients to complete and provide to the doctor prior to their appointment. The tool helps patients and families recognize changes over time and not to neglect these symptoms. It also serves as a prompt for doctors to make referrals for speech and swallowing.



Southeast/Richmond PADRECC Update (continued)

Education News

Report from Parkinson's Disease Consortium Conference and World Parkinson Congress

Four staff members from Richmond/Southeast PADRECC were in attendance at the National VA Parkinson's Disease Consortium Conference on September 19, 2016, followed by the 4th World Parkinson Congress from September 20-23, 2016 in Portland, Oregon. In attendance were Dr. Jessica Lehosit (Director), Peggy Roberge (Clinic Nurse Coordinator), Lynn Klanchar (Associate Director of Education), and Miriam Hirsch (DBS Nurse Coordinator). The National PD Consortium meeting was hosted by the Portland/Northwest PADRECC and included Directors and leadership from the other five PADRECC plus Consortium Center Directors and invited national and VACO speakers. This knowledge based face to face conference was successful in helping to meet short and long range program needs as well as the alignment with the VHA strategic plan. The Deputy National Director of Neurology at VA Central Office provided an update about the PADRECC and specialty care services budget and re-alignment plan. The meeting brought together movement disorder specialty leaders in the VA helping to strengthen the delivery of care for Veterans with movement disorders across the VA healthcare system. The one day consortium conference examined a variety of clinical care topics specific to PADRECCs: Duopa therapy; current strategies on drug-induced Parkinsonism; gastrointestinal symptoms and treatment approaches in PD; non-pharmacologic, integrative treatments including nutritional modifications, mindfulness and yoga. The conference provided continuing education accreditation for eight contact hours for doctors and nurses. A poster session at the end of the day allowed sharing among attendees about research projects and process improvement projects happening in the individual PADRECCs. Lynn Klanchar and Miriam Hirsch presented the poster "Staying Connected to Veterans with Deep Brain Stimulation" which demonstrated a systematic approach to case management that improves follow up care, maximizes the potential of DBS, minimizes adverse events, educates patients and caregivers, and emphasizes two-way communication for DBS surgical patients at Richmond/Southeast PADRECC.

The four day World Parkinson Congress (WPC) was successful in creating a worldwide dialogue to discuss the multifaceted problems of PD and propose solutions. It is the only meeting in the field of PD that addresses a need to bring the whole PD community (health care providers, researchers, patients and families) together for high-level scientific sessions and discussion on current work being done to advance science, improve care for people with PD, and help sensitize researchers to the needs of people with PD, and conversely help people living with PD understand the challenges research and health professionals face in their effort to find a cure and offer better care. The activity was planned and implemented in accordance with Accreditation Council for Continuing Medical and Nursing Education and other disciplines and provided 30.25 continuing education credits. There were plenary sessions for all and parallel sessions and workshops related to basic science, clinical science and comprehensive care.

Research News

DBS Advancements: Frameless & Fiducial-less DBS surgery, plus Quantitative (Q) EEG

Dr. Kathryn Holloway and her team are conducting numerous research projects at the Richmond PADRECC aimed at improving how deep brain stimulation (DBS) is performed and its clinical outcome. Two projects of particular interest include the comparison of fiducial vs fiducial-less DBS surgery and the use of quantitative electroencephalogram (QEEG) during DBS programming.

DBS surgery was first approved in the United States in 1997 for the treatment of tremor and several years later for the treatment of Parkinson's disease. At that time there was only way to implant a DBS lead which involved the use of a stereotactic head frame. This frame keeps the patient's head immobilized during the procedure. While it is cumbersome and can be frightening to patients, it is still used by many surgical centers today. Dr. Holloway and her colleagues developed a frameless system which is as accurate as the framed approach. The use of bone markers or fiducials replaced the frame in this type of surgery. Dr. Holloway has further improved frameless DBS by doing away with fiducials all together. She now performs frameless, fiducial-less DBS surgery and has demonstrated that it is as accurate as fiducial based DBS.

Southeast/Richmond PADRECC Update (continued)

The second project of interest involves the study of the brain's electrical activity during DBS programming using a quantitative electroencephalogram (QEEG). A QEEG is a non-invasive test that measures and records the electrical activity of the brain using special sensors. Dr. Holloway is particularly interested in the cortical responses to DBS stimulation of various regions of the basal ganglia and whether or not there is any correlation with cognitive status and improvement in motor symptoms.

For more information about these and other DBS related studies being conducted at the Richmond PADRECC, please call Miriam Hirsch, DBS coordinator at (804) 675-6284.

MJFF funded study currently enrolling, investigating eye movements in movement disorders

Dr. Mark Baron and colleagues continue ongoing research for their \$1 million Michael J Fox Foundation grant. This is a multi-center, double blinded study designed to investigate the possibility of predicting clinical diagnoses by way of measuring eye movements. The study is actively recruiting elderly controls, subjects with PD, and subjects with other movement disorders that may be mistaken for PD. Enrollment is approximately one third complete, and subjects are actively being recruited at the Richmond VAMC PADRECC, Virginia Commonwealth University, Emory University, and the University of Iowa. This has been an ongoing research interest at the Richmond PADRECC for over 8 years now, with very promising results to date. Current data suggest the ability to utilize eye movements to predict clinical diagnoses, and may significantly aid in the differential diagnoses of these conditions in the future. Recruitment in the study is ongoing, and the team hopes to conduct a preliminary analysis of the data this summer. In addition to clinically established movement disorder patients, this study also aims to recruit subjects with REM sleep behavior disorder, in order to determine if eye movements may be capable of predicting those who will develop PD later in life. Preliminary data suggests that eye movement recordings are capable of detecting preclinical stages of PD, at least 6 years in advance of the appearance of outwardly visible symptoms. For more information, please contact George Gitchel PhD, at george.gitchel@va.gov, or visit the funded study page at: https://www.michaeljfox.org/foundation/grant-detail.php?grant_id=1508

"Staying Connected" Poster Presented at World Parkinson Congress

Lynn Klanchar, Associate Director of Education (r) and Miriam Hirsch, DBS Nurse Coordinator (l) teamed up to develop a poster for the World Parkinson Congress (WPC) held September 20-23, 2016 in Portland, Oregon. The poster "Staying Connected to Veterans with Deep Brain Stimulation" highlighted a systematic approach to managing the 222 Veterans who have had DBS surgery and follow up at the Richmond PADRECC. 70% of Veterans with DBS live out of state, so case management and database maintenance is vital for keeping contact information accurate, arranging yearly follow ups, and keeping track if they get treatment from multiple sources.

This process improvement plan described strategies that have been ramped up to keep Veterans engaged and educated in self-care, safe from battery depletion, and not lost to follow up. Optimizing DBS treatment included: reinforcing the steps of DBS battery maintenance, educating about risks of hospitalization, increasing awareness about disease progression, referring to physical and speech therapists, providing medical alert bracelets, registering on My Healthy Vet to use Secure Message portal (encrypted electronic communication), and quarterly offering of a DBS only telephone support group. At Southeast PADRECC in FY 16, 92% of Veterans with DBS had a follow up visit in the past 12 months; 41% have used Telehealth; and 46% use secure messaging. The poster was among the top 25% selected to be part of a guided poster tour at the WPC, allowing Miriam and Lynn an opportunity to interact with a people from around the nation and world interested in quality care for patients with DBS.

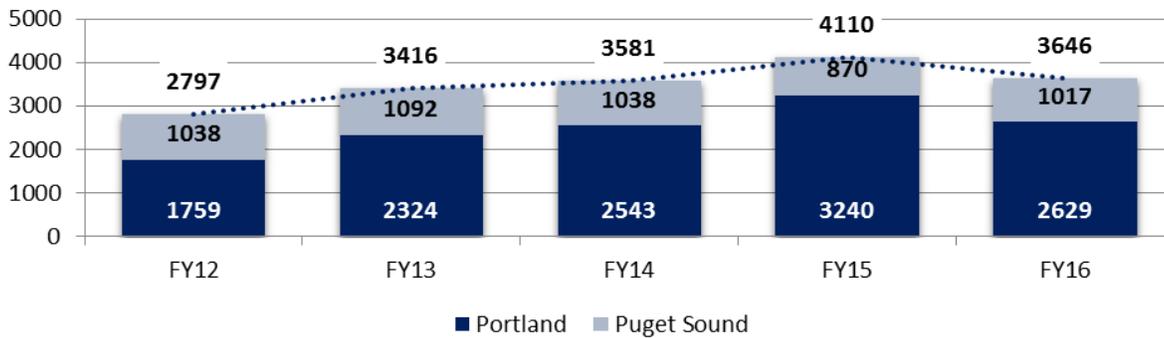


Northwest PADRECC Update

Clinical News

The NW PADRECC (Portland and Puget Sound), continue to support Veteran care by providing multi-faceted clinical care. The Portland clinic includes both movement disorder specialists, social work support, and psychiatric care. Not only are the Portland clinicians providing excellent movement disorder specific care, they also hold Neurotoxin clinics once a month for dystonia, tics, and headache/migraines. Clinical encounters have steadily increased since FY12 (See Figure 1).

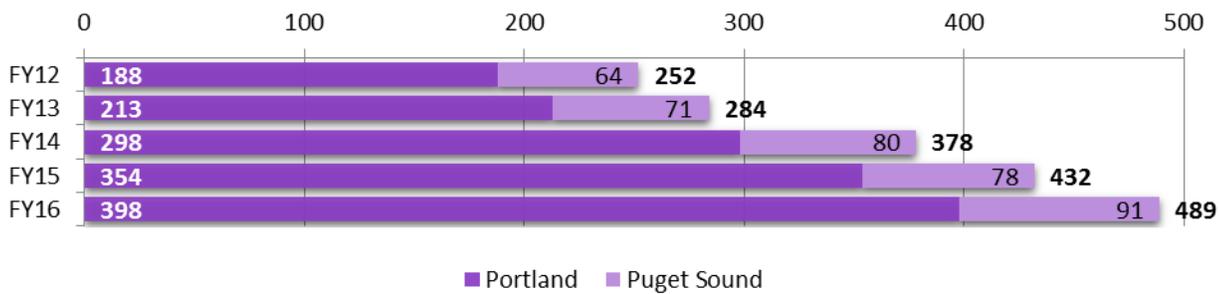
Figure 1. NW PADRECC Clinical encounters for the FY12-FY16 fiscal years.



Data Source: CDW Region 1 Corporate Data Warehouse (r01scredwh58.r01.med.va.gov), CDWWork, Outpatient 2.1 Domain, StopCode 335, Sta3n = 648 or 663. Removed Research (PAD RESEARCH) and Educational (PAD GROUP EDU-CVT) encounters.

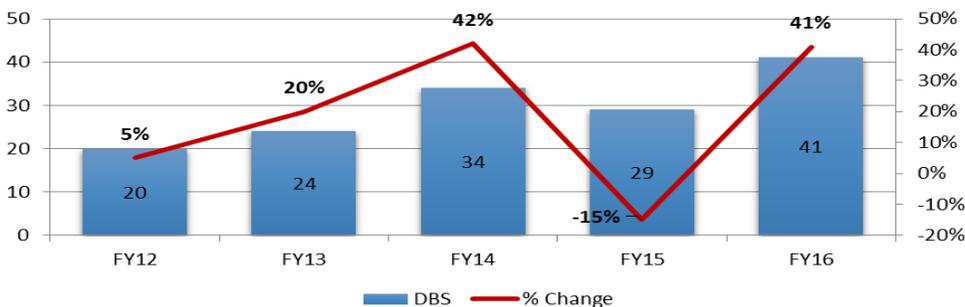
Although there was a slight decrease in FY16 with the loss of a full-time movement disorder specialist, clinical encounters are expected to remain high rising in FY17. In FY16, the NW PADRECC saw a 14% increase in Neurotoxin visits (figure 2), Portland saw a 41% increase DBS surgeries/battery replacements (figure 3), and a 27% telehealth visits

Figure 2. NW PADRECC Neurotoxin Encounters FY12-FY16.



Data Source: CDW Region 1 Corporate Data Warehouse, CDWWork, Outpatient 2.1 Domain, Portland StopCode = 335 (primary and secondary), Clinic Names containing Injection or Specialties or Spasticity. Puget Sound Primary StopCode = 335 encounters with CPT codes in 646.x, 902.x, J05.x.

Figure 3. DBS Surgeries (Portland PADRECC only) FY12-FY16.



Data Source: Maintained List

Northwest PADRECC Update (continued)

Telehealth Update

In addition to a growing clinical population, the Portland PADRECC has continued to expand telehealth to the Consortium Catchment area. The Portland PADRECC now conducts weekly telehealth clinics to Veterans who are unable to travel to the Portland area for an in-person clinical visit. The Portland PADRECC provides clinical telehealth to 21 different facilities in 2 different VISNs and 4 states (See map of telehealth consults received for FY16).

In FY 17 so far, NWPADRECC has had close to 160 TH visits. NWPADRECC uses our TH for new visits as well as follow up care.

TH has been used also for pre-DBS screening and post DBS care. We have educated our consortium members from Montana with TH and DBS programming. We have been able to do initial and follow up programming education with the provider and patient with excellent results.



Education News

NWPADRECC continues to provide educational conferences 4-5 times per year. These conferences are provided locally and are now V-tel'd out to 18 remote sites. We have built a strong network of dedicated TCT's who are committed to making this process work to provide educational information in an interactive environment for the patients who would not be able to access these conferences otherwise. The lectures are one hour long with a 30 minute question and answer session that all sites can participate in. The conference information is coordinated with the local TCT's and the lecture slides are provided to them ahead of time to share with the participants. Each site also has the participants fill out an evaluation form we provide them. This gives us excellent feedback on how this process is working and what topics patients are interested in. These are invaluable to assist us in planning so we can get the information out there that patients want to hear about.

Research News

The NW PADRECC strongly encourages investigator-initiated research projects. The Portland PADRECC has supported six of these projects in the past year and continues to support junior and senior faculty in original research projects. Some of the project in the past year have been:

Dyskinesia: Dr. Kathryn Chung's "Reducing Dyskinesia in Parkinson's Disease with Omega-3 Fatty Acids (funded by CSR&D Pilot Merit Grant)" which enrolled 30 levodopa naïve Parkinson's patients for a year and a half year longitudinal study. Participants were randomized to receiving docosahexaenoic acid or placebo and were examined for onset of dyskinesia using an objective device.

Stress Reduction: Dr. Amie Hiller's pilot projects, "Video-Based Mindfulness-Based Stress Reduction (unfunded)" and "Measuring Cortisol in Persons with Parkinson's Disease (funded by the Parkinson's Center of Oregon Pilot Grant)". Dr. Hiller's projects sought to examine the usefulness and feasibility of using video guided mindfulness-based therapies to reduce stress in Veterans and their caregivers.

Psychogenic Movement Disorders: Dr. Joel Mack's "Psychogenic Movement Disorders (unfunded)". This project examines functional movement disorders in relation to other movement disorders and other psychogenic disorders. Dr. Mack's project has resulted in one abstract and is currently being drafted for a manuscript.

Radiologic & Retrospective studies: Dr. Christopher Way's (fellow) investigator initiated studies, "Etiologies of the Hot Cross Bun Sign (unfunded)" and "Blood Pressure fluctuations in Parkinson's disease (unfunded)". Both studies are retrospective in nature and make use of the VA's unique ability to support research. They also demonstrate the NW PADRECC's support of investigator-initiated novel research.

Northwest PADRECC Update (continued)

Cognitive: In addition to local investigator-initiated projects, the Portland PADRECC continues to collaborate with the Puget Sound PADRECC on the “Pacific Northwest UDALL Center” which has enrolled 800+ Parkinson’s disease patients and controls (600+ at Puget Sound and 200+ at the Portland VA). This project is examining the long term cognitive changes in Parkinson’s disease. A sub-project, headed by OHSU’s Fay Horak PhD, examines gait and balance in a subset these participants.

Basic Science: Dr. Steven Johnson continues his basic science approach to compare effects of AMP kinase activation on postsynaptic membrane conductance and synaptic transmission in neurons in the VTA, substantia nigra, and subthalamic nucleus in slices of rat brain (funded by VA Merit Review Grant).

Why do you want to do some thinking while you exercise?

Fay B Horak, PhD, PT, Supervisory Research Scientist

People with Parkinson's' disease (PD) have specific types of cognitive (i.e.; thinking) problems, as well as specific types of mobility (i.e.; balance and walking) problems. For example, quickly inhibiting a response or quickly switching from one action to another has been shown to be difficult for those who have freezing of gait, or the feeling that their feet are “glued to the floor”. In addition, progression of cognitive dysfunction and progression of mobility disability seem to track together in both people with, and without, PD as they age. The associations between thinking dysfunction and mobility dysfunction may be related to shared brain circuitry in the frontal lobe for both cognition and mobility.

A new study at the Portland VA Health Care System is asking whether mobility exercises can improve thinking, as well as mobility. We first designed a novel Cognitive Agility Boot Camp in which a small group of participants spend 90 minutes at 6 different exercise stations that challenge both mobility and cognition. The photos, below, show examples of the stations: fast walking, large-aerobic movements, lunges, agility course, boxing and tai chi. Each of the stations also add cognitive challenges as participants improve with practice. Cognitive challenges include reading colors and not names of words, saying every other letter of the alphabet, responding to quick instructions, and quickly stopping a motion (such as a boxing punch). Balance, gait, cognition, and brain circuitry were evaluated before the exercise intervention, after 6 weeks of exercising, 3 times per week, and after 6 weeks of education and meditation.



Northwest PADRECC Update (continued)

Results with the first 29 subjects, all who had complaints of freezing of gait, are being presented at the Annual Movement Disorders Meeting in Vancouver, British Columbia June 5-8. The results show significant improvement in the ability to walk quickly while subtracting by threes after participating in the Boot Camp, but not the education/medication intervention. Freezing of gait, measured with body-worn sensors, improved most in the subjects who started with the worst freezing scores. Brain imaging also showed significant changes in connectivity of the circuit important for both mobility and response inhibition between the frontal cortex and the locomotor area in the brainstem on the right side. Future analysis will determine whether other aspects of cognition and mobility also improved. An ongoing study with 80 participants will determine whether the Cognitive Agility Boot Camp also helps people with PD who do not have freezing of gait.

The lesson from studies like these is that exercises that involve learning a new skill that challenge both mobility and cognition may be helpful for people with PD. Examples of such exercises include skills like learning ballroom dancing and Tai Chi or a sport like juggling or pickle ball. These types of exercises are also fun and can be enjoyed with friends and family so exercise can become part of, and enhance, daily life for many years to come.

NWPADRECC Udall Center Grant and Project

Dr Joseph Quinn, NWPADRECC Director

The Northwest PADRECC provides the infrastructure for a large, multi-center NIH-funded study aimed at understanding cognitive changes in Parkinson's disease. The NIH funds 9 "Udall Centers" for the study of Parkinson's disease, named after Arizona Congressman Morris K. Udall, who served in the US House of Representatives for 30 years, including 12 years after his diagnosis of Parkinson's disease in 1979, retiring in 1991. Each Udall Center funds "Core" function to promote Parkinson's research, as well as 3-4 "Projects" aimed at testing specific ideas. Udall Centers are funded on a competitive basis, which has to be renewed every 5 years. With only 9 Centers among more than 100 academic medical centers in the US, the process is highly selective.

The "Pacific Northwest Udall Center" was originally funded in 2010 as a collaboration between the Puget Sound and Portland VA Medical Centers and their affiliated academic centers, University of Washington and Oregon Health and Science University. In 2016, Stanford University was added to the collaboration, which was re-named the "Pacific Udall Center".

Since its founding, the Pacific Udall Center has characterized over 700 patients with Parkinson's, including extensive cognitive testing and genetic analysis. This has led to a focus on genes that are associated with cognitive impairment and dementia in Parkinson's disease, and has in turn led to design of the three projects currently being conducted by the Center. The project in Seattle is focused on advanced MRI studies to understand how the brains of Parkinson's patients with these genes differ from one another. The project in Portland is focused on how these genes affect gait and balance, as well as brain activity characterized by a method called "transcranial magnetic stimulation." The project in Stanford compares brain autopsy findings among Parkinson's patients with different genes.

Cognitive decline in Parkinson's disease is a major cause of disability and reduced quality of life. The lessons to be learned from the Pacific Udall Center are expected to improve our abilities to prevent and treat this aspect of Parkinson's disease, with the goal of improved outcomes and enhanced quality of life for our Veterans and for other patients.

Houston PADRECC Update

Clinical News

Houston's Parkinson's Disease Research, Education and Clinical Center (PADRECC) housed in the Michael E DeBakey VA Medical Center continues to provide state of the art medical and surgical services to Veterans with Parkinson's disease and related movement disorders who reside in the Southcentral and Midwestern United States.

Growth in Clinical Encounters

Annual comparison of the time periods between May 1-April 30 within FY2013–2017 shows an average increase in patient encounters of 12% for all PADRECC Clinics combined. Within that, there was an increase of 13% in the Clinician Movement Disorder Clinics, 23% in Neurotoxin Clinics, and 2% in Deep Brain Stimulation (DBS) Clinics. (Figures 1 and 2a-d). [Figure 2a excludes 576 nurse visits in the preceding cycle (May 1, 2015–April 30, 2016)]

Figure 1

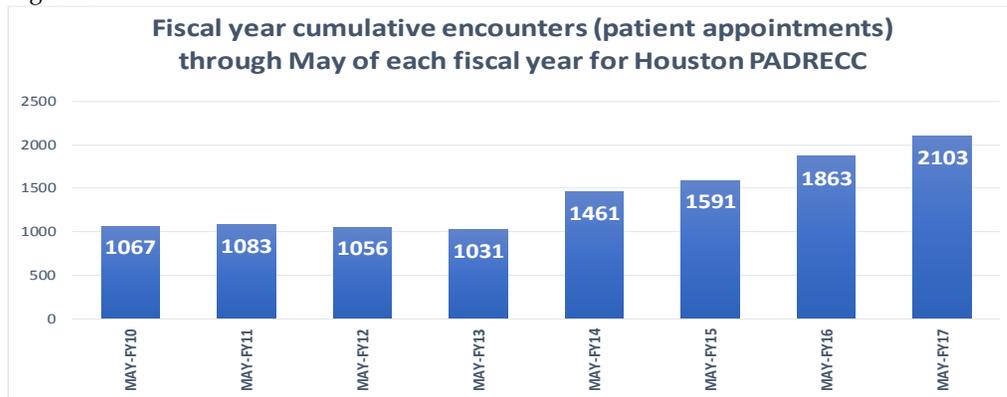


Figure 2a

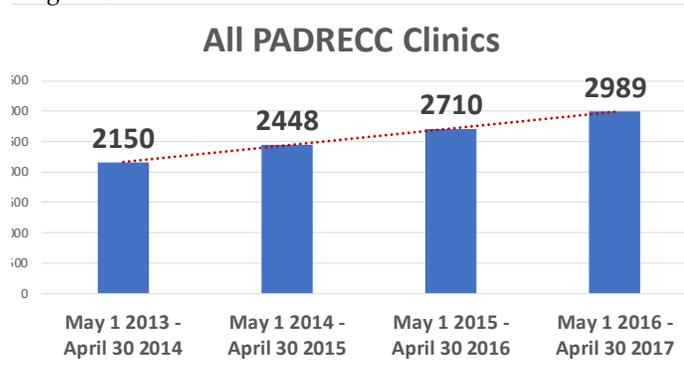


Figure 2b

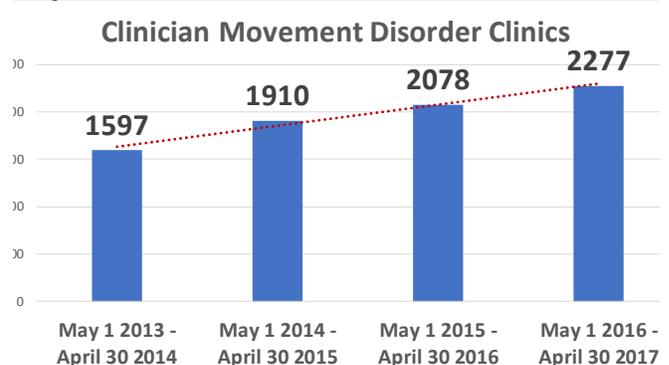


Figure 2c

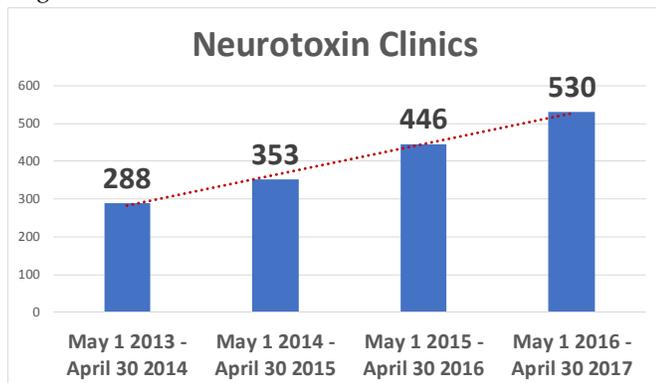
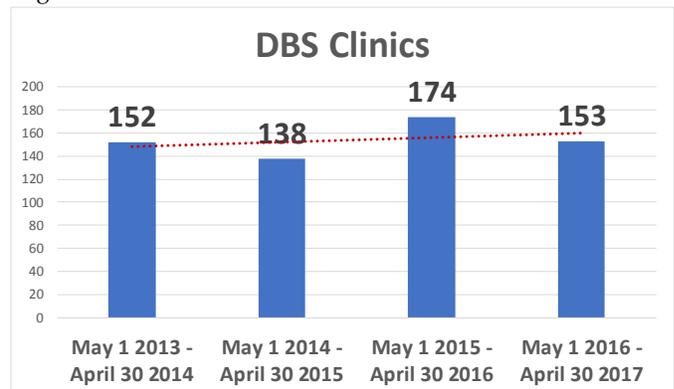


Figure 2d



Houston PADRECC Update (continued)

Deep Brain Stimulator Implantations

For the period from May 1, 2016 to April 30, 2017, we performed 7 DBS surgeries (5 bilateral and 2 unilateral), compared to 11 DBS surgeries (10 bilateral and 1 unilateral) in FY16, a 36% decrease. Both conventional and frameless techniques are being used. Our efforts on an initiative with the Departments of Neurosurgery to make the DBS surgery under sedation available to our patients are ongoing.

PADRECC Telehealth Expansion

PADRECC telehealth clinic appointments are now available with 4 of our community clinics (CBOC) within the Greater Houston Area, (Katy, Richmond, Lufkin, and Conroe). Patients who request or prefer to be seen closer to their homes, can now be seen via video-conferencing equipment connecting the community clinics with our PADRECC physicians. The five remaining CBOC clinics will be added to the PADRECC Telehealth network pending negotiation of time slots and completion of training by remote telehealth support staff.

Staff Recruitment—Clinic RN

We are in the process of recruiting a nurse to fill the current vacancy.

Palliative Care Clinic

The Palliative Care Clinic (PCC) has been restructured and will be in full operation following the recruitment of our vacant nurse position.

Education News

Patient Directed Clinic Based Education

Education is an essential component of the clinic visits at Houston PADRECC and is available to all patients and their care providers five days a week. It consists of: (1) One-on-one education by verbal instruction, to include education regarding DBS programmer, DBS care and safety; (2) Educational videos; and (3) Provision of relevant educational material [brochures, booklets, CDs].

Monthly Patient and Caregiver Educational Support Group

The monthly educational support group meetings are now being conducted as a teleconference. The teleconference takes place on the first Thursday of each month from 12:30 pm to 1:30 pm CST. The shift to this venue has allowed for easier access and has broadened the reach of this educational activity. Glennys Asselin-Cavey, Associate Director of Education, continues to lead the group. Aliya I. Sarwar, MD provides a question and answer session during the call. Guest speakers are invited to the support group. Various educational topics are discussed; information about our current local activities is disseminated. Participants effectively interact and learn from each other's experience. Patient feedback is obtained for continued quality improvement.

Collaboration with Psychiatric Pharmacy Residency Training Program

Houston PADRECC continues its collaboration with the Psychiatric Pharmacy Residency Training Program that was initiated in 2016. One pharmacy resident is expected per year; the first trainee has completed her rotation.

Collaboration with the Department of Veterans Benefits' Vocational Rehabilitation Program

From September 2015 to September 2016, as a part of a collaborative agreement with the Department of Veterans Benefits' Vocational Rehabilitation Program, Houston PADRECC provided clinical training to a Certified Nurse Assistant, who acted as a valuable resource for our clinical team. Under the same program, a Nurse Practitioner has begun her training at the Houston PADRECC as of 05/31/2017. She will be assisting the clinical and research work groups.

Nurse Education Initiative

This educational initiative continues at the Houston PADRECC. Educational lectures for FY 2017 to date:

- | | |
|----------|---|
| 10/25/16 | "Constipation and Parkinson's Disease", by Glennys Asselin-Cavey, MSN, RN |
| 12/20/16 | "Memory and Thinking Problems", by Sally Samuel, BSN, RN |

Houston PADRECC Update (continued)

Medical Professionals Based Educational Initiatives

Houston PADRECC's educational programs include: 1) Journal Club presentations; 2) Inter-disciplinary case presentations and discussion; (3) Live lectures featuring PADRECC or guest faculty; and 4) Audio lectures.

VA or Community Lectures

VA EES Movement Disorder Series: Houston PADRECC Neuropsychologist, Michele York, PhD, gave a well received presentation, on May 11, 2017, entitled: "Creativity in Parkinson's Disease".

Medical Faculty Lectures: On September 23, 2016, Dr. Sarwar gave a lecture to the Baylor College of Medicine Department of Neurosurgery, entitled: "Local Field Potential in DBS". Earlier that month, on September 19, 2016, Dr. Sarwar presented "Update on DBS Therapy" to attendees of the National PADRECC Consortium Conference in Portland, Oregon.

Community Lecture: Michele York, PhD gave a presentation entitled: "Defining Dementia in Parkinson's Disease" to the caregivers of persons with PD at the sixth annual Parkinson's Caregiver Conference held on November 19, 2016 by the Houston Area Parkinson Society (HAPS).

Medical Trainees Program

Mandatory clinical elective for senior (PGY4) Neurology residents from Baylor College of Medicine (BCM) continues at the Houston PADRECC. Aliya I. Sarwar, MD, PADRECC director, is the rotation mentor and director of the clinical course. During FY2017, the center trained ten Neurology residents in the phenomenology, diagnosis, medical and surgical management of Parkinson's disease, and other movement disorders. Residents are offered an opportunity to observe DBS surgery and learn the basics of DBS programming. Movement disorders research opportunities were made available to the BCM residents.

Update on Consortium Based Education and Clinical Activities

Membership: In line with the Houston PADRECC's initiative to expand its consortium outreach, we successfully added one additional member from Kansas.

Monthly Consortium Calls: We continue to host monthly educational consortium calls where our director leads the clinical discussion, providing the clinical and educational support to the consortium members.

National VA Parkinson's Disease Consortium Conference: The Houston PADRECC participated in the 2016 conference in Portland, Oregon. Dr. Sarwar was one of the faculty members involved in planning and carrying out conference activities. She gave a presentation entitled "An Update on DBS Therapy" and participated in the question and answer session that followed.

Community Participation

Michele York, PhD presented "Defining Dementia in Parkinson's Disease" at the sixth annual Parkinson's Caregiver Conference presented by the Houston Area Parkinson Society (HAPS) on November 19, 2016.

A PADRECC education booth was manned during the conference and educational handouts were made available. Educational videos from the "My Parkinson's Story" video series were played for the participants' educational experience.

Educational Newsletters

Houston's patient and family based newsletter, "PADRECC Pathways" topics for FY 2017 are: 1) *Sleep and Parkinson's Disease* by Aliya I. Sarwar, MD, Winter 2016 and 2) *Blood Pressure Changes in Parkinson's Disease* by Fariha Jamal, MD Spring 2017.

Research News

A Prospective, Randomized Placebo Controlled Pilot Study to Characterize the Intestinal Microbiome and to Evaluate the Safety and Fecal Microbiome Changes Following Weekly Administration of Lyophilized PRIM-DJ2727 Given Orally in Subjects with Parkinson's Disease— Limited studies have found fecal flora disturbances in PD. Dr. Sarwar is collaborating with the University of Texas School of Public Health and Kelsey Research Foundation in this pilot study that will completely

Houston PADRECC Update (continued)

characterize the microbiome in this group of subjects and evaluate microbiota replacement treatment as a means of flora restoration.

Prevalence of High-Resolution Manometric Abnormalities of the Esophagus and of Gastroesophageal Reflux in Patients with Parkinson's Disease—Dr. Sarwar is collaborating with investigators in the Dept. of Medicine/Division of Gastroenterology to launch this pilot project that aims to assess UES, esophageal body and LES function in PD patients using high resolution esophageal manometry and the presence and severity of acid and non-acid reflux using 24 hour pH/impedance monitoring. It will compare the physiological findings among patients with different stages of PD, between patients with and without dysphagia or GERD and age matched control subjects without PD undergoing manometry and 24 hour pH during the same time period.

Circadian Rhythm and Sleep in PD—This study, led by Dr. Sarwar, focuses on circadian rhythm and characterization of sleep patterns in Veterans with PD. A total of 210 subjects have been recruited. To augment previously collected scale and questionnaire data, a funded pilot study collected objective data on a subset of subjects, utilizing a wristwatch-like device to record movement/activity (actigraphy) and laboratory based melatonin measures from saliva (Dim Light Melatonin Onset). Future work will involve development of methodology for home-based saliva collection in PD study participants to expand the data collection to those patients who cannot travel to the facility sleep lab for overnight collection. A poster, "Leg Discomfort and Insomnia in Parkinson's Disease", was presented at the 2017 meeting of the American Academy of Neurology.

Analysis of Human Basal Ganglia Electrophysiological Recordings and Targeted Stimulation for Optimization of Deep Brain Stimulation—This ongoing collaborative project between the Houston PADRECC, Baylor College of Medicine and University of Houston is designed to analyze human electrophysiological data collected during deep brain stimulator or pulse generator (IPG, battery) implantation on PD or ET patients while simultaneously stimulating with various stimulation parameters such as contacts pairs, voltage and frequency, and then observing the effects of the stimulation in the target structures and correlating with changes in the symptoms of the patient. The goal is to allow one to understand the real-time effects of stimulation on the target structure, and drive the stimulation module adaptively, setting the framework for individualized therapy.

Longitudinal Study of Chronic TBI in OEF/OIF/OND Veterans/Service Members—Houston PADRECC continues to participate in this VA funded multi-center collaborative project designed to characterize the long-term effects of TBI on cognition, neuroimaging, and functional outcome in Veterans and service members who have been deployed to Iraq or Afghanistan. Additionally, the role of specific genes (catechol-O-methyltransferase (COMT), apolipoprotein E (APOE), and brain derived neurotrophic factor (BDNF) on cognition and functional outcomes are being explored.

Feasibility of Home Exercise and Walking Program to Promote Physical Activity in Veterans with Parkinson's Disease—The primary goal of this collaborative project is to obtain feasibility data evaluating the efficacy of a home exercise and walking program (HEWP) with phone or clinical video telehealth into the home (CVTHM) coaching to increase physical activity in sedentary Veterans with PD. The secondary goal is to study the effects of physical activity on mobility and functional ability in Veterans with PD. Six subjects have been recruited so far.

Effect of Resistance Exercise on Tremor and Hand Dexterity of Parkinson's Disease—The study looks at the effect of progressive resistance exercise on manual dexterity and tremor in persons with Parkinson's disease. The subjects receive training at the research site but perform the required 6 weeks of progressive resistance exercise of hand and arm at home.

Vitamin Deficiency and PD—This study uses medical record review to characterize vitamin D deficiency in those PD patients who have been screened for vitamin D deficiency and to describe the use and frequency of vitamin D testing in this patient population. A poster, "Vitamin D Deficiency and Severity of Parkinson's Disease in Veterans" was presented at the World Parkinson Congress in Portland, Oregon in September 2016 and another poster, "Vitamin D and Clinical Phenotypes of Parkinson's disease" was presented at the Movement Disorders Society meeting in Vancouver in June 2017.

Palliative Care for Veterans with Parkinson's Disease—An application for local MEDVAMC seed grant funding, was submitted in June 2017 and is under review. Data gathered from this pilot study will help to design a larger, prospective clinical trial to develop and validate an integrated, multidisciplinary model of care for advanced PD.

San Francisco PADRECC Update

First-of-Its-Kind Teleneurology Rotation for Residents at the San Francisco VA

Nicholas B. Galifianakis, MD, MPH – PADRECC San Francisco

Last year, the VA Office of Rural Health (ORH) funded an extra neurology resident position at the San Francisco VA (SFVA) to set up a new teleneurology training rotation. Nicholas Galifianakis, MD, Assistant Professor of Neurology at the University of California San Francisco (UCSF) and movement disorders neurologist at the SFVA PADRECC, whose career focus has been clinical research in telemedicine for PD, was asked to lead the efforts to develop and launch this novel resident rotation. This exciting development allows Neurology at the SFVA to build on VA's mission to expand access to Veterans, especially those who experience significant travel burden; both from geographic distance and neurological disability. It also gives UCSF neurology residents (who all rotate through the SFVA) an opportunity to learn more about an aspect of patient care that is both cutting edge and an inevitable and invaluable part of future of health care delivery.

Now, each UCSF neurology resident will spend 4 weeks of their residency training rotating through VA neurology clinics (e.g. the PADRECC, the Epilepsy Center of Excellence, the ALS clinic, and general neurology clinics), caring for Veterans exclusively via telemedicine technology. In the first two-week block, residents learn through didactics about teleneurology, hands-on practice with different telemedicine modalities and software platforms, and primarily learn through clinical experience, providing care to Veterans via "virtual house calls" (directly into patient homes) and clinic-to-clinic encounters (known as VTEL's at the VA), as well as performing remote e-Consultations. In the second two-week block, during their final year of training, they either contribute to ongoing teleneurology research projects, help develop or expand new clinical teleneurology services at the VA, or develop their own plan as to how they will implement telemedicine technology in their own future careers. With this comprehensive training, UCSF/SFVA neurology residents are already significantly expanding access to rural Veterans. They are also poised to be future leaders in developing new, innovative models of neurological care delivery using technology.

Expansion of Telehealth Clinics

Susan L. Heath, RN MS CNS – PADRECC San Francisco

VA PADRECC-SF Telehealth clinic visits with the State of California Veterans' Home, Yountville, CA was established in 2016 and continues to thrive. The SF-Yountville model has been used for a VA Telehealth relationship with the State of California Veterans Home in Redding, CA. A remote general neurology clinic will be established and PADRECC-SF will offer movement disorders Telehealth visits.

VA California providers interested in understanding steps to creating VA Telehealth with California State Veterans' Homes can call Susan Heath at PADRECC-SF (415) 379-5530.

Parkinson's Disease Palliative Care Clinic

Maya Katz, MD - PADRECC San Francisco

The Parkinson's Disease Supportive Care Clinic at the San Francisco PADRECC Center of Excellence was the first Parkinson's disease Palliative Care Clinic in the United States. Started 7 years ago, we continue to be pioneers in the delivery of interdisciplinary care focusing on alleviating the tremendous symptom burden associated with this illness to improve quality of life, align treatments with patient preferences, and reduce caregiver stress. Our experience with providing primary palliative care of those with Parkinson's disease and related disorders is already forming efforts to spread this type of care to academic medical centers and community neurologists through several national and international grants.

For example, VA PADRECC-SF neurologists are starting a 5-year study that has been funded by the NIH to provide a palliative care model for Parkinson's disease that can be widely disseminated. This study will assess the effectiveness and feasibility of a novel community-based intervention that empowers community neurology practices to improve care for Parkinson's disease patients and caregivers through primary palliative care training, coaching and telemedicine resources. The primary palliative neurology training program for the NIH grant will be directed by the Education in Palli-

San Francisco PADRECC Update (continued)

ative and End-of-Life Care (EPEC) education initiative. This training will also be a part of a larger online course available in conjunction with a textbook on neurology primary palliative care.

iMRI research

Maya Katz, MD - PADRECC San Francisco

Physiology-guided deep brain stimulation (DBS) surgery requires patients to be awake during a portion of the procedure, which is poorly tolerated by some patients. Interventional MRI-guided (iMRI) DBS surgery was developed by SFVA PADRECC Neurosurgeons Dr. Philip Starr and Dr. Paul Larson to use real-time image guidance, obviating the need for patients to be awake during lead placement. The primary reasons for choosing iMRI DBS is a preference to be asleep during implantation due to: 1) a history of claustrophobia; 2) concerns about the potential for discomfort during the awake physiology-guided procedure in those with an underlying pain syndrome or severe off-medication symptoms; or 3) non-specific fear about being awake during neurosurgery.

The SFVA is the first to formally study iMRI implantation using a stronger 3T magnet. Prior publications have used the 1.5T magnet, which is less applicable to most neurosurgical sites, which use the 3T magnet. Understanding the intricacies of this system using this more advanced magnet allows this groundbreaking technology to be used at a greater number of centers across the country to provide state-of-the-art care to individuals with Parkinson's disease.

Currently, the iMRI research study has completed data collection for its first 4 enrolled subjects and continues to enroll new subjects. To date, patients enrolled in this study have had comparable improvement in motor symptoms compared to the more traditional physiology-guided DBS lead placement.

Speechvive

Maya Katz, MD - PADRECC San Francisco

Parkinson's disease has traditionally been viewed as a disease of movement, but we now know that the most significant and disabling symptoms are the non-motor issues. Speech is markedly impaired for most people with Parkinson's disease after about 5-10 years of disease duration. Primarily, this impaired speech is characterized by a hypophonia that makes it very difficult, and eventually impossible to hear what individuals with Parkinson's disease are saying. This markedly contributes to the social isolation and disability experienced by those with this disease. As of January 2017, we are now offering the FDA approved Speechvive device, which uses a natural phenomenon called the Lombard effect to double the volume of patient's voices using a small externally wearable device.

Parkinson's Support Group: Shake-it-up-Baby!

Annie Li Wong, NP – PADRECC San Francisco

The San Francisco Parkinson's Support Group is a community group of about 40 patients and caregivers from all over the Bay Area who meet once a month at the SF VA. PADRECC advanced practice nurses Susan Heath and Annie Li-Wong co-lead the Parkinson's patients and our Chaplain, Carolyn Talmadge, leads the caregiver discussions.



The SF PD Support Group joined the National Parkinson's Foundation MOVING DAY Walk in San Francisco for the third year in a row. Captains Susan Heath, CNS and Annie Li Wong, NP lead their "SHAKE IT UP BABY" team to 6th place in fundraising. Their dedication to raising awareness for Parkinson's disease raised almost \$10,000.

San Francisco PADRECC Update (continued)

Cortical Physiology of Deep Brain Stimulation on Motor Circuits in Parkinson's Disease

Philip A. Starr, MD, PhD, PADRECC San Francisco

While the patterns of neuronal loss in Parkinson's disease have been well described, the manner in which neuronal loss alters brain circuitry to produce the cardinal motor signs of Parkinson's disease has not been clear. The Starr lab work has revealed specific patterns of neural activity underlying the signs and symptoms of Parkinson's disease (PD). We introduced powerful technical approaches for understanding circuit-level brain dysfunction in PD: electrocorticography, high-resolution, high-signal recordings from leads placed directly on the brain surface during surgery. We have used this technique to demonstrate an abnormal state of neuronal synchronization in the motor cortex, that is related to slow movement in Parkinson's disease. We showed that an important mechanism of therapeutic deep brain stimulation is reversal of this abnormal pattern.

My Parkinson's Story

Susan L. Heath, RN MS CNS, PADRECC San Francisco

Created by all six PADRECCs, The VA YouTube playlist: *My Parkinson's Story* consists of twenty short educational segments told through the grace of individual Veterans' stories. The PADRECC program is very pleased at how useful these videos have become for patients, caregivers, providers and educators.

Deep Brain Stimulation and Parkinson's disease

Early Parkinson's disease

The impact of depression in Parkinson's disease

Thinking and Memory Problems with Parkinson's disease

Impact of Falls and Parkinson's disease

Sleep Problems and Parkinson's disease

My Parkinson's Story: Advanced Parkinson's

My Parkinson's Story: Driving

My Parkinson's Story: Exercise

My Parkinson's Story: Hospitalization

My Parkinson's Story: Impulsive Behavior

My Parkinson's Story: Medications

My Parkinson's Story: The Caregiver

My Parkinson's Story: Speech and Swallowing

My Parkinson's Story: Genetics

My Parkinson's Story: Environmental Exposure

My Parkinson's Story: Atypical

My Parkinson's Story: Dyskinesias

My Parkinson's Story: Pain

My Parkinson's Story: Visual Disturbances

The highest viewed story is the *Advanced Parkinson's* story, a San Francisco filmed segment.

This is a direct link to the playlist :https://www.youtube.com/playlist?list=PL3AQ_IVoBEyxd5tkfOG-S3p_SDYBFtJ6c

Southwest PADRECC Update

Greater Los Angeles Healthcare System

The West LA VA Medical Center provides subspecialty care to patients with Parkinson's disease and other movement disorders, in addition to training two PADRECC Special Fellows in our field each year.

Under the leadership of PADRECC Director, **Dr. Indu Subramanian**, the West LA VA Movement Disorders clinic has expanded, adding two new physicians and a new Nurse Care Manager this year.

Dr. Adrienne Keener, MD is a Movement Disorders Neurologist who joined the team after completing her fellowship as a PADRECC VA Special Fellow in the Spring of 2016. She is an Assistant Professor at UCLA with an interest in epidemiology in Parkinson's Disease, working with Drs. Jeff Bronstein and Beate Ritz on the longitudinal Parkinson's Environment and Gene (PEG) Study. At the VA, she runs the botulinum toxin clinic and is working to bring telehealth to Veterans in the Greater LA Healthcare System. She is also interested in medical education, and serves as the Associate Program Director for the UCLA Neurology Residency Program.

Dr. Denise Feil, MD, MPH is a geriatric psychiatrist and associate professor of health sciences at UCLA who joined the West LA VA Movement Disorders clinic in the Fall of 2016. She has extensive experience working in integrative care programs, including Greater Los Angeles VA's GRECC (Geriatric Research, Education and Clinical Center), Memory Clinic, and HIV/Infectious Disease. She received a VA HSR&D Career Development Award and Diabetes QUERI RRP for research related to degenerative cognitive disorders and individualized care of vulnerable elderly patients. She is actively involved in training psychiatry residents and fellows in geriatric psychiatry. She joins the PADRECC to integrate targeted psychiatric services into the Movement Disorders program, support and build cross-disciplinary education and training of psychiatry and neurology residents and fellows on Movement Disorders, and to support PADRECC's program development and health services research.

Patricia Pittman, RN, MBA joined the West LA VA team in June 2017 as a full-time Nurse Care Manager. She has a wealth of experience working in the VA and other health systems in areas including bed control, utilization review, and clinical outcomes. She brings an enthusiasm for working with neurologic patients with a prior background coordinating care for the Neuromuscular, ALS and Multiple Sclerosis clinics in the Greater LA Healthcare System. We are happy to welcome her to the team!

The West LA VA Neurosurgery department also recruited a new functional neurosurgeon, **Dr. Ausaf Bari, MD, PhD**, who joined **Dr. Jean-Philippe Langevin** in July 2016 providing surgical treatments for patients with movement disorders. Dr. Bari completed his fellowship training in Toronto with Dr. Andres Lozano, where he studied the relationship between the motor and reward systems of the brain, and the use of deep brain stimulation (DBS) to modify and enhance them.

Research Update:

The Greater Los Angeles PADRECC health services team, led by **Drs. Karen Connor and Eric Cheng** are analyzing a 5-year randomized controlled trial of a nurse-led care management/care coordination program, designed and implemented across VISN 22 and funded by VA HSR&D. The nurse-led program, "Care Coordination for Health Promotion and Activities in Parkinson's Disease" (CHAPS), is guided by a set of 38 Parkinson's disease quality indicators, chosen by a task force of movement disorder specialists, nurses, and community members. These PD indicators were chosen for most room for improvement and highest validity (a critical component of good care). A total of 345 subjects enrolled across Greater Los Angeles, Las Vegas, Loma Linda, Long Beach, and San Diego VA health care systems. Subjects were randomly assigned on a 1:1 ratio to either intervention arm or control arm (usual care). Primary outcomes are adherence to PD indicators, indicating better quality of care provided. Secondary outcome measures provide information of patient effects in this trial. The trial concluded in April 2017; analysis is currently underway. Results are expected to be available in Fall 2017.

Southwest PADRECC Update (continued)

San Diego Healthcare System

Dr. Stephanie Lessig and **Marcy Ticachek, RN** run the PADRECC clinic in San Diego. The Neurology Service at the San Diego VA Medical Center, La Jolla offers a monthly Parkinson's Multidisciplinary Clinic. This clinic joins cognitive, rehabilitation, and neurology services into one clinic visit. The San Diego VA also offers telehealth services for patients who live at a distance and are not able to attend in-person clinic appointments.

Marcy Ticacheck, RN is the CHAPS Nurse Care Manager and participated in the study *"Improving Quality of Care in Parkinson's Disease: A Randomized Controlled Trial,"* headed by Dr. Karen Connor. She has been instrumental in the process of translating this research intervention into an ongoing clinical program at the San Diego VA.

The Neuropsychology Service at the San Diego VA offers a VA support group for persons with Parkinson's Disease. In addition, **Drs. Stephanie Lessig and Fatta Nahab** present an annual PD patient symposium, as well as an annual provider symposium directed at non-movement disorder providers such as primary care physicians and nurse practitioners.

Dr. Lessig is the site Co-Principal Investigator at UCSD for the nationally recognized PPMI study by the Michael J Fox Foundation that targets newly diagnosed Parkinson's patients throughout the community, including the VA.

Albuquerque Healthcare System

Dr. Sarah Pirio-Richardson, a movement disorders specialist, and **JoAnn Harnar, RN** run the PADRECC clinic in Albuquerque, New Mexico. Clinical activities include specialty care for patients with tremor, ataxia, Parkinson's disease and dystonia. Botulinum toxin injections and deep brain stimulation programming are done for patients in VISN 18 from eastern Arizona, southern Colorado, New Mexico and western Texas. Teleneurology and nurse education sessions are important parts of these services.

JoAnn Harnar, RN has taken the lead as the coordinator for the monthly PD @ Home telephone support group.

In July 2017, **Dr. Richardson** came on board full-time at the VA. In moving to the VA, her goal is to develop a joint neurostimulation research program for movement disorders, including Parkinson disease, and psychiatric conditions with the VA psychiatry program. In addition, she is one of two North Americans chosen for the 2017 MDS LEAP program. The MDS LEAP Program has been established to provide a leadership training program to support the growth, development and success of young movement disorder specialists while maximizing their contributions to the goals and objectives of the International Parkinson and Movement Disorder Society (MDS). The LEAP Program is an 18-month program encompassing the development of leadership skills through a mentored development and a didactic skills format.

Las Vegas Healthcare System

Dr. Selina Parveen provides movement disorder, deep brain stimulation and botulinum toxin management to a large catchment area in Nevada, Arizona and Utah in VISN 22. She often is a guest speaker at the community support group, Friends of Parkinson's, in which many Veterans attend. She is also the site Principal Investigator for the study led by Dr. Karen Connor, *"Improving Quality of Care in Parkinson's Disease: A Randomized Controlled Trial"*.

Loma Linda Healthcare System

Dr. Dorothee Cole manages the movement disorder clinic at the VA in Loma Linda, CA, which provides specialty care for patients with Parkinson's disease including deep brain stimulation programming and Duopa pump programming. She also administers botulinum toxin injections for various kinds of dystonia and treats other movement disorders such as ataxia and tremor. She also is the Loma Linda site Principal Investigator for the multi-center VISN 22 study, *"Improving Quality of Care in Parkinson's Disease: A Randomized Controlled Trial,"* headed by Dr. Karen Connor at the West Los Angeles VA.

Maribel Padua, PhD, a geropsychologist in the Primary Care Mental Health Integration Clinic, Loma Linda VA also offers a unique Parkinson's disease support group for both caregivers and Veterans. The four week program meets every Friday and includes a Lee Silverman Voice Treatment session with the speech pathologist, both Veteran and caregiv-

Southwest PADRECC Update (continued)

er breakaway sessions with the psychologist and social worker, and singing as a speech exercise strategy at the end. Dr. Cole and other neurologists provide guest talks. For more information, contact Dr. Padua at (800) 741-8387, x4890.

Long Beach Healthcare System

Dr. Steven Schreiber is Chief of Neurology at the VA Long Beach Healthcare System where he oversees the local PADRECC and was instrumental in developing the first Teleneurology programs in the VA system. He also serves as local Principal Investigator for PADRECC-related studies, including Dr. Karen Connor's study on *"Improving Quality of Care in Parkinson's Disease: A Randomized Controlled Trial."*

Dr. Sandeep Thakkar is a movement disorders specialist who provides subspecialty care for patients with Parkinson's disease and other movement disorders, including Duopa and DBS programming. He runs a Saturday Movement Disorders clinic at the Long Beach VA for those patients who are unable to come in during regular weekday hours.

Megan Gomez, PhD, a licensed clinical psychologist in the Primary Care Mental Health Integration Clinic, who specializes in neuropsychology and neurodegenerative diseases, facilitates a monthly Parkinson's Support Group at the Long Beach VA. Started in February 2016 in an effort to improve the quality of life for Veterans with Parkinson's, the support group has a focus on non-motor symptoms of Parkinson's disease. Guest speakers include Psychologists presenting on mindfulness/meditation for PD and cognitive changes in PD, Kinesiotherapists presenting on PWR! For PD, Speech-Language Pathologists presenting on Lee Silverman Voice Therapy (LSVT) for PD, among others. For more information, contact Dr. Gomez at (562) 706-0740.

Tucson, Southern Arizona Healthcare System

Scott Sherman, MD, PhD and his research laboratory focus on developing novel therapies for Parkinson's disease (PD) and have several translational research projects. His research led to the discovery that neurotrophic factors, Vascular Endothelial Growth Factor-B and a PEDF, a factor derived from the retina, are neuro-protective. Basic laboratory studies in these areas are continuing. Another line of research explores the use of low-dose ketamine for the treatment of PD dyskinesia. Preclinical work in the laboratory has shown that low-dose ketamine can prevent the development of dyskinesia in an animal model of Parkinson Disease. Recent human studies have shown that ketamine given at low doses can improve depression and pain. These findings open the door to study the potential of low-dose ketamine treatment for patients with PD that have dyskinesia, neuropathic pain, and depression, all of which are common comorbidities. Plans are underway to begin a small clinical trial next year.

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