



THE TRANSMITTER

March 2018

Article Reviews

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Vitamin B12 and homocysteine levels predict different outcomes in early Parkinson's disease

In patients with moderately advanced Parkinson's disease, it is known that low B12 levels can be associated with neuropathy and cognitive impairment. However, vitamin B12 deficiency had not been studied in early Parkinson's disease. In this study, patients with early, unmedicated Parkinson's disease were assessed to determine the prevalence of B12 deficiency and if this correlated with lower scores on the MMSE (Mini Mental Status Examination). Data came retrospectively from patients from the DATATOP study (1987-1988). 680 early Parkinson's patients had B12, methylmalonic acid, homocysteine, and holotranscobalamin serum levels collected. Subjects were evaluated every 3 months for up to 24 months, and at each visit they were assessed for disability sufficient to require levodopa therapy (the primary endpoint of DATATOP) and for secondary outcomes including the MMSE, total UPDRS and its subscores. At later visits, serum labs were again drawn for comparison. At baseline, 13% of patients had borderline low B12 levels (<184pmol/L, with low B12 considered <157pmol/L), 7% had elevated homocysteine levels (>15 umol/L), and 2% had both. Notably those with borderline low or low B12 levels did not consistently have changes in MCV on basic hematologic studies. Patients with borderline low and low B12 levels that persisted over time developed greater morbidity; they had about twice as much decline in terms of ambulatory capacity score (derived from UPDRS subscores of gait and postural stability) when compared to those with normal B12. Interestingly, elevated homocysteine was associated with lower MMSE scores at baseline and predicted greater declines in MMSE, independent of B12 levels. This supports prior evidence that homocysteine may play a role in cognitive decline over time. The authors concluded that in early Parkinson's disease low B12 is common and predicted greater worsening of mobility, while elevated homocysteine levels predicted greater cognitive decline. Given B12 deficiency is treatable, screening and treatment could potentially impact progression and improve quality of life over time in patients with early Parkinson's disease.

Movement Disorders Clinical Practice. 2018 March

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<https://doi.org/10.1002/mds.27301>

Selected health and lifestyle factors, cystosine-adenine-guanine status, and phenoconversion in Huntington's disease

Huntington's disease (HD) is an autosomal-dominant associated with a CAG trinucleotide repeat mutation of the huntington gene. Although the increasing number of CAG repeats is correlated with earlier disease onset and increased disease severity, there is well-known incomplete penetrance with a range of variable phenotype severities observed in patients with the same repeat number. The Prospective Huntington At-Risk Observational Study (PHAROS) which is an ongoing effort through the Huntington's Study group is working to identify factors which may affect disease progression by prospectively following a group of pre-symptomatic individuals genetically at-risk for HD. This recent study looked specifically at several modifiable lifestyle and health-related factors to identify if any of them were associated with earlier phenoconversion to symptomatic HD. 247 PHAROS participants completed at least 1 environmental survey to self-report use of various exposures including tobacco, alcohol, caffeine, medications, and head injury. Results of this study demonstrated the 36 (14.6%) subjects phenoconverted to symptomatic HD during the study period after they completed the environmental survey. The regular use soda consumption was significantly associated with phenoconversion (P= .05), there was also a significant association with higher current and cumulative soda consumption

($P=.0376$ and $P=.06$ respectively). There was interestingly no significant association with other caffeinated beverages. The use of tobacco or alcohol or any other medications were also not associated with increased risk of phenoconversion nor was history of head injury. While this study does not prove a causative link between HD phenoconversion rate and consumption of soda, it does provide areas for further research as we continue to look for ways to modify the course of this disabling disease.

Mov Disord, 2018 March; 33(3) 472-478

<https://onlinelibrary.wiley.com/doi/full/10.1002/mds.27239>

Pesticide use in agriculture and Parkinson's disease in the AGRICAN cohort study

Previous studies have suggested a link between pesticide exposure and increased risk of Parkinson's disease, but it is unknown what kinds of pesticides might have the greatest risk and what length of exposure is needed. The AGRICAN study followed a group of 181,000 French farmers and measured their exposure to pesticides by taking into account reports of exposure to certain crops as well as pesticide use at work. Lifelong pesticide use was associated with an increased risk of Parkinson's disease and certain crops, such as peas, and specific pesticides, such as rotenone, had the strongest association with a diagnosis of Parkinson's disease. While this study strengthens the link between pesticide exposure and Parkinson's disease, results should be interpreted cautiously, since exposure to pesticides was calculated based on patient report, which can be unreliable, and diagnosis of Parkinson's disease was also based on patient report, not examination by a neurologist. The researchers plan to follow this group to see who develops Parkinson's disease over time.

International Journal of Epidemiology. 2018; 47:299-310

Pouchieu C, Piel C, Carles C et al. Pesticide use in agriculture and Parkinson's disease in the AGRICAN cohort study.

Committee Activities

Clinical Care Committee

- **Rotation of Committee Chair:** Leadership for the clinical care committee rotates amongst the PADRECCs. The San Francisco PADRECC leads the committee for March/April. The committee meets via conference call the first Tuesday of the month at 12pm (EST)
- **Standardize and Optimize Clinical Care:** The committee continues to discuss latest research on PD, new treatment strategies and a variety of clinical issues to improve patient care and outcomes. It also serves to provide clinical support to the consortium network by focusing on measures to standardize clinical care across the PADRECC network. Recent agenda items have included discussions on:
 1. New medications deutetrabenazine and valbenazine for Huntington's chorea and tardive dyskinesia.
 2. The management of orthostatic hypotension including the role of the newly FDA-approved agent droxidopa (Northera).
 3. Continued discussion focused on clinical experience sharing among the group regarding DUOPA™ (carbidopa and levodopa) enteral suspension delivered directly into the small intestine for the treatment of motor fluctuations for people with advanced Parkinson's disease
 4. The prevalence of vitamin D deficiency in Parkinson's disease and the need to monitor and adequately replete levels for bone and cognitive health.
 5. Practical aspects regarding the use of DAT scans; applications and pitfalls, including the issue of drug interference
 6. Continued discussion on the use of Pimavaserin (Nuplazid) in the treatment of psychosis associated with PD, compared to quetiapine and clozaril.

7. Continued discussion of Rytary and conversion and titration dosing strategies. Consensus that often more than a three times/day dosing is needed.
8. Discussion of the possible role for levodopa-induced hyperhomocystinemia in Parkinson's disease and the strategies to monitor and manage this problem
9. Discussion of the role of exercise in the treatment of PD and the practical aspects of "prescribing" exercise to patients.

Education Committee

- **2018 National VA PD Consortium Conference:** Conference is being held on April 20, 2018 at the Westin Hotel LAX prior to the American Academy of Neurology (AAN) meeting. RSVP deadline is April 7, 2018 to Dawn McHale (dawn.mchale@va.gov).
- **PADRECC/EES Movement Disorder Series:** The third audioconference for FY 18 was held on March 8th, 2018, "Tardive Dyskinesias" by Nijee Luthra, MD PhD, San Francisco PADRECC & UCSF. The audioconferences are archived on the National website www.parkinsons.va.gov under the Movement Disorder Series tab. Please see the **Dates to Remember** section below for a listing of upcoming FY17 audioconferences and mark your calendars.
- **PD at Home:** Monthly PD telephone education/support group conference available nationwide on the 2nd Tuesday of each month: 10am PT, 11am MT, 12p CT, 1pm ET. Monthly flyers will be emailed to all Consortium Members, please advertise to your PD patients.
- **National Website Maintenance:** The committee performs monthly maintenance checks of the National Website to ensure information is current and up-to-date.
- **PADRECC Transmitter:** This committee continues to assemble and distribute this e-newsletter every other month.
- **Resources available on the National Website- *Please share with your patients***
 - **Updated Patient Education Brochures-** <https://www.parkinsons.va.gov/patients.asp>
 - Exercise and Physical Activity
 - Fall Prevention
 - PD Medications
 - Motor Symptoms
 - Non-Motor Symptoms
 - Agent Orange and Toxic Exposures and PD
 - **My Parkinson's Story-**<https://www.parkinsons.va.gov/patients.asp>
A series of short videos prepared by the VA PADRECCs addressing various aspects of Parkinson's disease.
 - **Suggested Education Essentials for Veterans with PD** <https://www.parkinsons.va.gov/patients.asp>
 - **PADRECC Support Group Listings** <https://www.parkinsons.va.gov/patients.asp>
 - **Updated Resource Request Form-**PADRECC and Consortium members can order bulk supply of FREE educational materials from PF and APDA. Please click on the following website and complete the Resource Request Form and mail or fax to address listed:
<https://www.parkinsons.va.gov/clinicians.asp>

Northwest PADRECC Updates

Director: Dr. Joseph Quinn

The Northwest PADRECC is comprised of the VA Portland Health Care System and the Puget Sound VAMC and consortium sites.

Activities:

- **Telehealth:** NWPADRECC Portland has a very active Telehealth clinic seeing 12-15 patients per month as both new evaluations, follow up care, and Pre-DBS screening.
- **DBS:** So far for FY 18 Portland has completed 10 DBS surgeries and 10 battery changes. We are currently all trained and are using the new St. Jude DBS system and just started using the Boston Scientific device for implantation.

We are also continuing to do programming of Veterans who come to us for the surgery from outside our VISN via TH with the home provider with the patient to control the programmer. This has saved multiple trips for these folks back and forth to Portland.

- **Botox:** Portland and Seattle continue to have very active botox injection clinics. We easily see over 500 visits per year. Staff was currently trained in the use of the ultrasound, useful for patient in need of injections for siallorrhea as well as spasticity.
- **Education:** Portland has hosted 2 patient education events for FY18:

“Exercise and Parkinson’s Disease: A Powerful medicine”, presented by Laurie King PhD, PT

“ Sleeping Challenges in Parkinson’s Disease” presented by Amie Hiller MD

Both conferences were held locally in Portland as well as sent out by V- tel to 12 remote sites. We had a total of over 200 participants!

- NWPADRECC Portland will be hosting its annual CME “**Neurology Updates for General Practice**”. This is offered locally as well as by V-tel to any health provider interested. The topics vary from year to year. This year the topic titles are: “NPH/What to Do?”, “Neuro-ophth/What Am I Seeing?”, “Neuro Causes of Autonomic Dysfunction”, and “Cannibis and Epilepsy”. Registration for this event is in TMS.

Publications FY18:

- **Chung K, Lobb B, Murchison CF, Maancini M, Hogarth P, & Nutt JG (2018). Assessment of an Objective Method of Dyskinesia Measurement in Parkinson’s Disease, Movement Disorders Clinical Practice, <https://doi.org/10.1002/mdc3.12583>**

Abstract: Background: The goal of this study was to validate an objective method of measuring levodopa induced dyskinesia in Parkinson’s disease (PD). Methods: To characterize agreement between the clinician-based measure and a force plate, we assessed dyskinesia in PD subjects participating in a randomized and blinded clinical trial of an adenosine A2A antagonist. Convergent validity and intra-class correlations were evaluated between the objective force plate measure and clinician assessments. Results: All measures correlated across time and detected differences in treatments. Conclusion: Our results indicate that objective measure from a force plate is in scale agreement with clinical ratings of dyskinesia severity, indicating it as a reliable method to measure LID objectively but with greater resolution to detect changes in LID.

- **Way C, Pettersson D, & Hiller A (2018). Etiologies of the ‘Hot Cross Bun’ Sign: A Retrospective Chart Review. Neurology Clinical Practice. Under Review**
- **Cholerton B, Johnson CO, Fish B, Quinn JF, Chung KA, Peterson-Hiller al, Rosenthal ls, Dawson TM, Albert MS, Hu SC, Mata IF, Leverenz JB, Poston KL, Montine TJ, Zabetian CP,**

& Edwards KL (2018). Sex Differences in Progression to Mild Cognitive Impairment and Dementia in Parkinson's Disease, Parkinsonism & Related Disorders, 2018 Feb 9. pii: S1353-8020(18)30043-9. doi: 10.1016/j.parkreldis.2018.02.007. [Epub ahead of print]

INTRODUCTION: Identification of factors associated with progression of cognitive symptoms in Parkinson's disease (PD) is important for treatment planning, clinical care, and design of future clinical trials. The current study sought to identify whether prediction of cognitive progression is aided by examining baseline cognitive features, and whether this differs according to stage of cognitive disease. **METHODS:** Participants with PD in the Pacific Udall Center Clinical Consortium who had longitudinal data available and were nondemented at baseline were included in the study (n = 418). Logistic and Cox regression models were utilized to examine the relationship between cognitive, demographic, and clinical variables with risk and time to progression from no cognitive impairment to mild cognitive impairment (PD-MCI) or dementia (PDD), and from PD-MCI to PDD. **RESULTS:** Processing speed (OR = 1.05, p = 0.009) and working memory (OR = 1.01, p = 0.03) were associated with conversion to PDD among those with PD-MCI at baseline, over and above demographic variables. Conversely, the primary predictive factor in the transition from no cognitive impairment to PD-MCI or PDD was male sex (OR = 4.47, p = 0.004), and males progressed more rapidly than females (p = 0.01). Further, among females with shorter disease duration, progression was slower than for their male counterparts, and poor baseline performance on semantic verbal fluency was associated with shorter time to cognitive impairment in females but not in males. **CONCLUSIONS:** This study provides evidence for sex differences in the progression to cognitive impairment in PD, while specific cognitive features become more important indicators of progression with impending conversion to PDD.

Active Research Projects:

- **Buspirone, in combination with amantadine, for the treatment of levodopa-induced dyskinesia (OHSU eIRB # 11875)**

Dr. Kathryn Chung is conducting a research study looking at the effect and the safety (side effects) of buspirone in combination with amantadine on abnormal involuntary movements (dyskinesias) in Parkinson's disease (PD). In order to take part in this study, participants must: have PD, take at least 200 mg of Amantadine a day, and started taking levodopa more than three (3) years ago. This study will last for 6 weeks with 4 of those weeks on study drug and require seven (3) visits to the VA Portland Health Care System. The first visit lasts approximately 2 – 3 hours and involves general physical, neurological, and Parkinson's disease specific examinations, and assessments of your abnormal movements. If you do not meet the criteria for abnormal movements in the study, you may not be randomized or receive study drug. You will then be given study drug (or placebo) and after two weeks, you will return to the Portland VA for a 6 hour study visit from 08:30 am to 2:30 pm. All participants will take the study drug (buspirone) and the placebo. This is a double-blinded study which means that you and the research staff will not know what study treatment you are taking at any point. You will not be compensated for participation in this study. This is a research study and not for treatment or diagnosis of PD. You may not benefit from participating in this study but will have a no cost neurological exam. However, by serving as a subject, you may help us learn how to benefit patients in the future. For more information on how to participate, please contact Brenna Lobb, Research Coordinator, at (503) 220-8262 extension 51871 or by mail at 3710 SW US Veterans Road, P3-PADRECC, Portland, Oregon 97239.

- **Pacific Northwest Udall Center (PaNuC): Clinical Core and Specimen Collection (VA IRB # 2332; OHSU eIRB # 6154)**

Dr. Joseph Quinn is conducting this research study to examine the changes in thinking and memory of Parkinson's disease patients over time. A second goal is to determine the role genetics plays in cognitive impairment in Parkinson's disease. You must have a diagnosis of Parkinson's disease to participate in this study or be willing to participate as a healthy control.

This is a long term study, your participation would last 5 years or more. The study involves at least two visits to the VA Portland Health Care System. At each visit, you will undergo tests of thinking and memory, have a neurological exam, fill out questionnaires, and have a blood draw of about four tablespoons. Each visit will last for about three to four hours. After the first visit, you have the option to undergo a lumbar puncture. A lumbar puncture is known as a spinal tap. A spinal tap is where a special needle is inserted between bones in your back and fluid is removed. The spinal tap will take about two to two and a half hours. You have the option to undergo a second spinal tap three years after the first spinal tap. You will be compensated \$200.00 for each spinal tap that you complete.

In between visits at the VAPORHCS you will have a telephone interview with questions regarding your thinking and memory. These interviews will last about 30 minutes.

This is a research study and not for treatment or diagnosis of Parkinson's disease. You may not benefit from participating this study. However, by serving as a subject, you may help us learn how to benefit patients in the future. For more information on how to participate, please contact Micki Le, BS, Study Coordinator at (503) 220 – 8262 extension 54688 or by mail at 3710 SW US Veterans Road, P3-PADRECC, Portland, Oregon 97239.

- **Using Multiplex Families to Map Genes that Modify Susceptibility and Age at Onset in Parkinson's Disease (VA IRB # 2731)**

Dr. Kathryn Chung is conducting this research study to identify genes that increase a person's risk of developing Parkinson's disease (PD) or related disorders. The goal of this study is to better understand and treat PD and other related disorders. If a gene or genes that cause(s) PD can be identified and characterized, the diagnosis and treatment of PD will be improved. The overall goal of this study is to find genes that increase the likelihood of developing Parkinsonian symptoms and certain PD-related problems, such as difficulties with thinking and memory.

You are eligible to participate in this study if you have Parkinson's disease, or have a participating family member with Parkinson's disease.

This study involves one visit to the VA Portland Health Care System Medical Center. At this visit, you will undergo a physical examination, questions about your family history, a brief test of thinking and memory and have a blood draw of about four tablespoons. This visit will last for about 2 1/2 hours.

This is a research study and not for treatment or diagnosis of Parkinson's disease. You may not benefit from participating this study. However, by serving as a subject, you may help us learn how to benefit patients in the future. There is no compensation for participation in this study. For more information on how to participate, please contact Brenna Lobb, MS MPH, Study Coordinator at (503) 220 – 8262 extension 51871 or by mail at 3710 SW US Veterans Road, P3-PADRECC, Portland, Oregon 97239.

- **Measuring Cortisol Levels in Persons with Parkinson's (PD) (VA IRB # 3794, OHSU eIRB # 15183)**

Dr. Amie Hiller is conducting a research study looking at cortisol levels in Parkinson's disease (PD). Cortisol is a hormone that is normally released in response to events and circumstances such as waking up in the morning, exercising, and stress. We are recruiting both Parkinson's disease patients and healthy controls. To be a healthy control, you must not have a neurological disorder. Both groups must be willing to give saliva samples. This study will last for approximately 1 week. There are two option paths for participation. Option 1 has three (3) days of saliva collection at home and one visit to the Portland VA (VA Portland Health Care System). Option 2 has two visits to the Portland VA. Visit one will last approximately 30 minutes and include questionnaires of mood and quality of life. For PD participants, a Parkinson's focused exam will be performed. You will collect your saliva, complete some diaries, and wear some sensors for three days at home. You will return to the Portland VA for a visit that lasts about five minutes to return the sensors, diaries, and saliva. The visit will last approximately 30 minutes and include questionnaires of mood and quality of life. For PD participants, a Parkinson's focused exam will be performed. You will not be compensated for participation in this study. This is a

research study and not for treatment or diagnosis of PD. You may not benefit from participating in this study. However, by serving as a subject, you may help us learn how to benefit patients in the future. For more information on how to participate, please contact Brenna Lobb, Research Coordinator, at (503) 220-8262 extension 51871 or by mail at 3710 SW US Veterans Road, P3-PADRECC, Portland, Oregon 97239.

- **A Phase 3, Open-Label Study of the Safety, Efficacy, and tolerability of Apomorphine Administered by Continuous Subcutaneous Infusion in Advanced Parkinson's Disease Patients with Unsatisfactory Control on Available Therapy [infusiON Apokyn] (VA IRB # 4202)**

***NEW** Kathryn Chung MD PI, Susan OConnor RN, Research Coordinator

- **Clinical Characteristics of Parkinson's Disease Subjects with Severe Hypertension During Motor OFFs (VA IRB # 4202)**

Dr. Kathryn Chung and Dr. Way are conducting a research study looking at blood pressure changes in Parkinson's disease (PD). This study involves two visits with one at-home monitoring period of a couple of days in-between the visits. The first visit, a screening visit, will happen at the VA Portland Health Care System and last about one hour. During this visit, you will complete some questionnaires, answer some questions about your Parkinson's disease and have a physical examination. You will then be sent home to monitor your blood pressure in relation to your levodopa dose cycle for the next couple of days. The second visit will last 4 to 8 hours depending on your levodopa cycle. You will arrive in the morning at 08:00 am in an "OFF" state. You will eat breakfast. Every half hour you will undergo various measures of your Parkinsonism, vitals, movements, and answer more questionnaires about how Parkinson's affects you. The study visit will last until 03:00 pm or when you turn "OFF". There is no compensation for participation in this study. You may not personally benefit from participating in this study. However, by service as a subject, you may help us learn how to benefit patients in the future. For more information on how to participate, please contact Brenna Lobb, Research Coordinator, at (503) 220 – 8262 extension 51871 or by mail at 3710 SW US Veterans Rd, P3-PADRECC, Portland, Oregon 97239.

Grants:

Active:

- Zabetian C 2017-2021 VA Merit Review Award, 1 I01 CX001702 (PI), "Genetic Movement Disorders: Etiologies and Pathogeneses"
- Zabetian C 2016-2021 NIH/NINDS, 1 U01 NS100610-01 (Co-I), "Dementia with Lewy Bodies Consortium"
- Samii A 2012-2018 Sponsor: CHDI Number: A-5807 (Site Investigator), "A Prospective Registry Study in a Global Huntington's Disease Cohort"
- Quinn J 2013-2018 NIH UH2/UH3 (Co-I), "Clinical utility of extracellular RNA for biomarker development".
- Quinn J 2014-2019 NIH/NCCAM, R01AT008099 (Co-I), "Mechanisms and Active Compounds in the cognitive effects of Centella Asiatica"
- Quinn J 2015-2020 NIH/NIA, P30 AG008017 (Biomarker & Genetics Core Leader), "Oregon Alzheimer Disease Center",
- Quinn J 2009-2020 NIH/NINDS, P50 NS062684 (Site PI), "Pacific Northwest Udall Center

- Quinn J 2011-2018 NIN / NINDS, 5U10NS077350-03 (PI), “Comprehensive Oregon Neuroscience Network for Excellence in Clinical Trials (CONNECT)”
- Johnson S 2015-2019 Veterans Affairs Merit Grant 1 I01 BX002525 (PI), “Regulation of VTA dopamine neurons by AMP kinase”
- Johnson S 2014-2018 USPH Grant 1 R01 DA038208-01 (PI), “Regulation of VTA dopamine neurons by AMP kinase”
- Chung K 2009-2020 NIH/NINDS, P50 NS062684 (Site Co-I), “Pacific Northwest Udall Center”

Submitted:

- Chung K “Preventing Levodopa Induced Dyskinesia in Parkinson’s Disease with Statins” CSR&D Merit Review
- Hiller A “A trail of tele-medicine based stress reduction program in Parkinson’s disease” R&RD Merit Review; Aging & Neurodegenerative Disease

Dates to Remember

April 20, 2018

National VA PD Consortium Meeting

Los Angeles, CA

April 21-27, 2018

American Academy of Neurology~ Annual Meeting

Los Angeles, CA

<https://www.aan.com/conferences/annual-meeting/>

May 10, 2018

EES/PADRECC Movement Disorders Series

Topic: Psychiatric Issues in Parkinson’s Disease

<http://www.parkinsons.va.gov/>

September 13, 2018

EES/PADRECC Movement Disorders Series

Topic: Neurotoxin use for treating PD Symptoms

<http://www.parkinsons.va.gov/>

October 5-9, 2018

International Parkinson and Movement Disorder Society (MDS)~International Congress

Hong Kong

<http://www.mdscongress.org/Congress-2018.htm>