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NATIONAL VA PARKINSON'S DISEASE
CONSORTIUM
Education · Collaboration · Advocacy

THE TRANSMITTER

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Article Reviews

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Pimavanserin for Parkinson's Disease psychosis: Effects stratified by baseline cognition and use of cognitive-enhancing medications

The antipsychotic pimavanserin is a selective serotonin 2A receptor inverse agonist, approved for treatment of psychosis in Parkinson's disease by the FDA in 2016. Using data from the pivotal randomized clinical trial of pimavanserin, this study aimed to evaluate the differential effect of this medication in patients with and without cognitive impairment, who were or were not also taking cognitive-enhancing medications, including cholinesterase inhibitors or memantine. The primary outcome was change in the PD-adapted Scale for the Assessment of Positive Symptoms (SAPS-PD). In patients with cognitive impairment (MMSE 21-24) who received pimavanserin, there was a larger improvement from baseline in the SAPS-PD compared to those without cognitive impairment (-6.62 vs -5.50). Furthermore, there was also a larger effect of pimavanserin in patients also taking cognitive-enhancing medications, though this did not reach statistical significance due to low power. These data suggest that the response to pimavanserin is robust in PD patients with cognitive impairment, and may possibly be further enhanced by concomitant use of cognitive-enhancing medications.

Mov Disord. 2018 Nov 2. doi: 10.1002/mds.27488.

Safety and Tolerability of Multiple Ascending doses of PRX002/RG7935, an Anti-Synuclein Monoclonal Antibody, in Patients with Parkinson's Disease

Aggregated a-synuclein is believed to be central to the pathogenesis of Parkinson's Disease. There is a profound need for disease modifying therapy in Parkinson's disease. Preclinical studies of a-synuclein monoclonal antibodies have demonstrated a decreased intracellular accumulation of a-synuclein in transgenic mice, with subsequent decreases in synaptic loss and gliosis. PRX002 is a humanized monoclonal antibody designed to target aggregated a-synuclein. Jankovic et al present this phase 1b multicenter, randomized, double blind, placebo controlled trial, designed to evaluate safety and tolerability of this antibody. Patients aged 40-80, with mild to moderate idiopathic PD (Hoehn and Yahr stage 3) were randomized to 6-ascending dose cohorts of PRX002 or placebo. The study included 80 participants, receiving 3 infusions, every 4 weeks and were monitored over a total period of 24 weeks. The study found no serious PRX002 related adverse events. PRX002 treatment emergent adverse events included constipation in (9.1%), infusion reactions(7.3%), diarrhea(5.5%), headache(5.5%), peripheral edema(5.5%), upper respiratory tract infection(5.5%) and post lumbar puncture syndrome(5.5%). No antidrug antibodies were detected. Serum PRX002 increased in a dose proportional manner. CSF PRX002 increased with dose at an approximate concentration of 0.3% of serum. Rapid dose-dependent reductions in serum free a-synuclein, up to 97% at highest dose, were observed after each infusion and maintained for longer at higher doses. No significant difference in CSF free a-synuclein was observed. Exploratory clinical assessments did not reveal any meaningful differences between placebo and treatment groups. The authors concluded that multiple doses of PRX002 were safe and well tolerated, thus supporting ongoing study of PRX002 in a phase 2 clinical trial.

JAMA Neurol. 2018 Oct 1;75(10):1206-1214. doi: 10.1001/jamaneurol.2018.1487.

Early predictors of mortality in parkinsonism and Parkinson disease
Previous studies of survival in Parkinson disease have been completed and suggest there are factors associated with increased mortality in PD, such as non-tremor predominant features, dementia, and early autonomic dysfunction. This paper examined risk factors for mortality in all new onset parkinsonism in a region of Northern Sweden. A total of 143 patients with idiopathic PD, 13 patients with multiple systems atrophy, 18 patients with progressive supranuclear palsy were followed prospectively for at least 8 years and up to 13.5 years. Patients with secondary parkinsonism and dementia at baseline, including dementia with Lewy bodies, were excluded. The results showed patients with atypical parkinsonism had the highest rate of mortality with a standardized mortality ratio of 3.32. In idiopathic PD, there was also significantly increased mortality compared to population controls with a standardized mortality rate of 1.58. However, when PD patients were separated by presence of mild cognitive impairment or normal cognition, only the group with cognitive impairment had a significantly increased mortality. There were also other factors associated with increased mortality including freezing of gait, severe hyposmia, reduced dopamine transporter activity in the caudate, and lymphocytosis in the CSF. Interestingly, tremor score and orthostatic blood pressure drop did not have a significant impact on mortality. This study adds to our knowledge of risk factors for mortality in Parkinson's disease.

Neurology. 2018; 00:e1-e12. e-published ahead of print.

Committee Activities

Clinical Care Committee

• **Rotation of Committee Chair:** Leadership for the clinical care committee rotates amongst the PADRECCs. The Portland PADRECC leads the committee for November/December. 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. Clinical experience with recently introduced medications for Parkinson's disease, Huntington's disease, and tardive dyskinesia including Rytary, Extended Release Amantadine, Pimavanserin, deutetrabenazine, valbenazine, etc.

2. Continued discussion about referrals, outcomes and target selection trends regarding deep brain stimulation surgery for PD, ET, and dystonia.

3. Continued discussion focused on clinical experience sharing among the group regarding DUOPA™ (carbidopa/levodopa) enteral suspension for the treatment of motor fluctuations in advanced Parkinson's disease

4. Discussion about newer avenues of delivering tele-health within the VA healthcare system including video-connect

5. Discussion about newer clinic models to provide focused treatment for non-motor symptoms of PD (Palliative Care Clinics) and to improve overall health of our patient population (Wellness Clinics)

6. Discussion about the role of kinesiotherapy in Parkinson's disease

7. Strategies to minimize the impact of reduced workforce at the PADRECC, innovative ideas to improve performance and deliver care

8. Discussion about collaborative research, including involvement in industry supported projects like Apomorphine subcutaneous infusion study.

9. The prevalence of vitamin D deficiency in Parkinson's disease, the need to monitor and strategies and outcomes of current replacement strategies.

10. Discussion about management of psychogenic/functional movement disorders

Education Committee

- **PADRECC/EES Movement Disorder Series:** The first audioconference for FY 19 was held on November 8th, 2018, **"Lewy Body Dementia"** by Joseph Quinn, MD, Portland PADRECC. 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 FY19 audioconferences and mark your calendars.
- **National VA PD Newsletter:** The 2018 newsletter can be reviewed on the national website: https://www.parkinsons.va.gov/Consortium/cfiles/Newsletters/VAParkinsonReport2018.pdf
- **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.
- **Updating PADRECC Pocket Card:** Committee is exploring updating the pocket card which includes the treatment algorithm and medication list as it is out of date. Project request submitted and approved by EES to help with design and distribution. Prospective project start date, January 2019.
- **National Website Maintenance:** The committee performs 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*
    - **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 staff and consortium members can order bulk supply of FREE educational materials from PF and APDA. Please click on the following website link and complete the ***Resource Request Form*** and mail or fax to address listed: https://www.parkinsons.va.gov/clinicians.asp

Southwest PADRECC Service Area Updates

Southwest PADRECC

Director: Dr. Indu Subramanian

The Southwest PADRECC is comprised of the Greater Los Angeles VA and consortium sites in Albuquerque, NM; Las Vegas, NV; Long Beach, CA; Loma Linda, CA; San Diego, CA; and Tucson, AZ.

Consortium Updates:

- West LA VA welcomed a new Administrative Officer to the team, Dessa Jones.
- Dr. Andrew Wilson also joined the West LA VA team following completion of a fellowship in Health Services Research. Dr. Wilson is working to develop a clinical dashboard to monitor quality of care indicators in Parkinson's Disease.
- Dr. An Tran, a fellowship-trained Movement Disorders specialist, joined the Long Beach VA consortium site and is working to expand access to subspecialty care there, including DBS programming and botulinum toxin injection procedures.

Consortium Activities:

- The Southwest PADRECC performed 17 Deep Brain Stimulation surgeries and 34 battery replacements in FY18, in addition to 5 Duopa Implantations.
- The West LA VA hosted its first multidisciplinary patient education seminar, Parkinson's disease 101.
- The West LA VA has implemented a new pharmacy-driven protocol to identify patients at risk for medication non-compliance, and the barriers that lead to non-compliance. The pharmacist is then able to provide education and counseling to the patients and their caregivers to improve quality of care.
- Dr. Scott Sherman's basic research laboratory at the Tucson VA is a major collaborator on an NIH-funded project to develop neuroprotective molecules in rodent models of Parkinson's disease.
- Dr. Sarah Pirio-Richardson of the Albuquerque VA conducts research in focal dystonia using transcranial magnetic stimulation to study metaplasticity in the human motor cortex.
- Dr. Indu Subramanian received board certification in Integrative Medicine, and hosted an international think tank to review the current evidence for use of these therapies in Parkinson's disease.
- Dr. Adrienne Keener is kicking off the West LA VA's first Movement Disorders Telemedicine clinic utilizing VA Video Connect, enabling us to reach patients in their homes.

Clinical Publications & Presentations:

PUBLICATIONS:

1. Pahwa R, Isaacson SH, Torres-Russotto D, **Nahab FB**, Lynch PM, Kotschet KE. Role of the Personal Kinetograph in the routine clinical assessment of Parkinson's disease: recommendations from an expert panel. Expert Rev Neurother. 2018 Jul 26:1-12. doi: 10.1080/14737175.2018.1503948

2. Bhattacharjee S, Vadiei N, Goldstone L, Alrabiah Z, **Sherman SJ.** Patterns and Predictors of Depression Treatment among Older Adults with Parkinson's Disease and Depression in Ambulatory Care Settings in the United States. Parkinson's Dis. 2018 Mar 1; 2018:3402983. doi: 10.1155/2018/3402983. eCollection 2018. PubMed PMID: 29686832; PubMed Central PMCID: PMC5852869.

3. Schreiber. S.S. Tele neurology for Veterans in a Major Metropolitan Area. Tele med JE Health. 2018 Sep;24(9):698-701.

PRESENTATIONS:

1. Jarrahi, B., Petkus, A. J., **Gomez, M. E.,** Filoteo, J. V., Schiehser, D., Hui, J., Petzinger, G., & McEwen, S. A Multivariate Analysis of the Effects of Physical Activity and Cognition on Resting-State Brain Networks in Parkinson's Patients with and without Mild Cognitive Impairment, (Poster presented at the Annual Meeting of the American Academy of Neurology, Los Angeles, CA, April 2018.)

2. Petkus, A. J., Filoteo, J. V., Schiehser, D., **Gomez, M. E.,** Jarrahi, B., Hui, J., McEwen, S., & Petzinger, G. Cognitive Performance and Symptoms of Anxiety, Depression, and Apathy in Parkinson's Patient with and Without Mild Cognitive Impairment, (Poster presented at the Annual Meeting of the American Academy of Neurology, Los Angeles, CA, April 2018)

3. Bina R, **Pirio Richardson S**, Langevin JP. Cheyne-Stokes respirations following deep brain stimulation. (Presented as a poster at the American Society for Stereotactic and Functional Neurosurgery Conference, Denver, Colorado, June 2018)

4. **Lessig S**, Marder SR, Verghese C, Burke J, Jimenez R, Siegert S, Liang GS. Global Improvement and Patient Satisfaction: Results from a Long-Term, Open-Label, Rollover Study of Valbenazine in Tardive Dyskinesia. (Movement Disorder Society, Oct 2018)

5. Barlas Y, Nesiba N, Quinn D, **Pirio Richardson S**. Metaplasticity in the human motor cortex: validation of a crossover experimental design. (Presented as a poster at the New Mexico Medical Conference, Santa Fe, 2018)

Research Publications & Presentations:

1. **Lessig S,** Rojas JC, Bang J, Lobach IV, Tsai RM, Rabinovici GD, Miller BL, Boxer AL; AL-108-231 Investigators CSF neurofilament light chain and phosphorylated tau 181 predict disease progression in PSP. Neurology. 2018 Jan 23;90(4): e273-e281. doi: 10.1212/WNL.0000000000004859. Epub 2017 Dec 27. PMID:29282336

2. Teves JMY, Bhargava V, Kirwan KR, Corenblum MJ, Justiniano R, Wondrak GT, Anandhan A, Flores AJ, Schipper DA, Khalpey Z, Sligh JE, Curiel-Lewandrowski C, **Sherman SJ**, Madhavan L. Parkinson's Disease Skin Fibroblasts Display Signature Alterations in Growth, Redox Homeostasis, Mitochondrial Function, and Autophagy. Front Neurosci. 2018 Jan 12;11: 737. doi: 10.3389/fnins.2017.00737. eCollection017. PubMed PMID: 29379409; PubMed Central PMCID: PMC5770791.

3. Caballero B, **Sherman SJ**, Falk T. Insights into the Mechanisms Involved in Protective Effects of VEGF-B in Dopaminergic Neurons. Parkinson's Dis. 2017; 2017: 263795. doi: 10.1155/2017/4263795. Epub 2017 Apr 3. Review. PubMed PMID: 28473940; PubMed Central PMCID: PMC5394414.

4. Singh A, **Pirio Richardson S**, Narayanan N, Cavanagh JF. Frontal midline theta is diminished during cognitive control in Parkinson's disease. *Neuropsychologia* 2018 May 23; 117:113-122. Doi: 10.1016/j.neuropsychologia.2018.05.020

5. Davis LE, Harnar J, Lachey-Barbee LA, **Pirio Richardson S**, Fraser A, King MK. Using teleneurology to deliver chronic neurologic care to rural veterans: analysis of the first 1,100 patients. *Telemed J E-health* 2018 Jul 17. doi: 10.1089/tmj.2018.0067

6. Chen NK, Chou YH, Sundman M, Hickey P, Kasoff WS, Bernstein A, Trouard TP, Lin T, Rapcsak SZ, **Sherman SJ**, Weingarten CP. Alteration of Diffusion-Tensor Magnetic

Resonance Imaging Measures in Brain Regions Involved in Early Stages of Parkinson's Disease. Brain Connect. 2018 Aug;8(6):343-349. doi: 10.1089/brain.2017.0558. PubMed PMID: 29877094; PubMed Central PMCID: MC6103245.

7. Ye T, Bartlett MJ, Schmit MB, **Sherman SJ**, Falk T, Cowen SL. Ten-Hour Exposure to Low-Dose Ketamine Enhances Corticostriatal Cross-Frequency Coupling and ippocampal Broad-Band Gamma Oscillations. Front Neural Circuits. 2018 Aug13; 2:61. doi: 10.3389/fncir.2018.00061. eCollection 2018. PubMed PMID: 30150926; PubMed Central PMCID: PMC6099120.

8. Flores AJ, Bartlett MJ, Root BK, Parent KL, Heien ML, Porreca F, Polt R, **Sherman SJ,** Falk T. The combination of the opioid glycopeptide MMP-2200 and aNMDA receptor antagonist reduced l-DOPA-induced dyskinesia and MMP-2200 by itself reduced dopamine receptor 2-like agonist-induced dyskinesia. Neuropharmacology.2018 Sep 7;141:260-271. doi: 10.1016/j.neuropharm.2018.09.005. [Epub ahead of print] PubMed PMID: 30201210

9. Holiday KA, Pirogovsky-Turk E, Malcarne VL, Filoteo JV, Litvan I, **Lessig SL,** Song D, Schiehser DM. Psychometric properties and characteristics of the north-east visual hallucinations interview *in Parkinson's disease.* Mov Disord Clin Pract. 2017 Sep-Oct; 4(5):717-723.

10. Lopez FV, Split M, Filoteo JV, Litvan I, Moore RC, Pirogovsky-Turk E, Liu L, **Lessig S**, Schiehser DM. *Does the Geriatric Depression Scale measure depression in Parkinson's disease?* Int J Geriatric Psychiatry. 2018 Sep 25. doi: 10.1002/gps.4970. [Epub ahead of print]

11. Cavanagh JF, Kumar P, Mueller AA, Pirio Richardson S, Mueen A. Diminished EEG habituation to novel events effectively classified Parkinson's patients. *Clinical Neurophysiology* 2017 129:409-418.

12. **Keener AM**, Paul KC, Duarte Folle A, Bronstein J, Ritz B. Cognitive Impairment and Mortality in Population-based Parkinson's disease Cohort. Journal of Parkinson's Disease 2018. doi: 10.3233/JPD-171257

PRESENTATIONS:

1. Barlas Y, Nesiba N, Quinn D, **Pirio Richardson S.** Metaplasticity in the human motor cortex: validation of a crossover experimental design. (Presented as a poster at the New Mexico Medical Conference, Santa Fe, 2018)

Under Revision, Submitted or in preparation:

1. Paul KC, Chuang YH, Shih I, **Keener A,** Bronstein J, Bordelon Y, Ritz B. Lifestyle Factors Influencing Progression and Mortality in Parkinson's Disease.

2. Duarte Folle A, Paul K, **Keener A**, Bronstein J, Ritz B. Clinical progression in Parkinson's disease with features of REM Sleep Behavior Disorder: a population-based longitudinal study.

3. GM Moreno, R Gandhi, **SL Lessig**, B Wright, I Litvan, **FB Nahab.** Mortality in Patients with Parkinson's Disease psychosis receiving Pimavanserin and quetiapine. Neurology (In press)

4. Landers with MR, Navalta J, Murtishaw A, Kinney J, **Pirio Richardson S.** A phase II, pragmatic, randomized clinical trial of a high-intensity exercise boot camp for Parkinson's Disease: feasibility, safety, safety, signal of efficacy, and disease mechanisms. (Accepted, Journal of Neurologic Physical Therapy.

Dates to Remember

January 10, 2019

EES/PADRECC Movement Disorders Series

Topic: Stimulating Memory in Parkinson's Disease: New Directions in Neuromodulation

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

March 14, 2019

EES/PADRECC Movement Disorders Series

Topic: Pain in PD

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

May 4-10, 2019

American Academy of Neurology (AAN) Annual Meeting

Philadelphia, PA

https://www.aan.com/conferences-community/annual-meeting/

May 9, 2019

EES/PADRECC Movement Disorders Series

Topic: Sleep Issues and PD

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

June 2-7, 2019

5th World Parkinson Congress

Kyoto, Japan

https://www.worldpdcoalition.org/default.aspx

September 12, 2019

EES/PADRECC Movement Disorders Series

Topic: Parkinson's 101

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