U.S. Department of Veterans Affairs
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Parkinson's Disease Research,
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NATIONAL VA PARKINSON'S DISEASE
CONSORTIUM
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THE TRANSMITTER

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Article Reviews

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Structural and molecular cholinergic imaging markers of cognitive decline in Parkinson's disease

Parkinson's disease (PD) is associated with progressive cognitive impairment that greatly impacts quality of life and contributes to disease burden. Emerging evidence suggests that cholinergic dysfunction underlies the cognitive decline in PD. Cholinergic system can be investigated in vivo via MRI-based volumetry of basal forebrain and PET scan measures of cortical cholinergic activity. Julia Schumacher and colleagues investigated the relationship between basal forebrain degeneration and PET-measured depletion of cortical acetylcholinesterase activity, as well their relative contribution to cognitive impairment in PD. They included 143 PD patients without dementia and 52 healthy controls. All participants underwent structural MRI brain, PET scanning with [^{11}C]-methyl-4-piperidinyl propionate (PMP) as a measure of cortical acetylcholinesterase activity, and a detailed cognitive assessment. Based on the 5th percentile of the overall cortical PMP PET signal from the control group, people with Parkinson's disease were subdivided into a normo-cholinergic (N=94) and a hypo-cholinergic group (N=49). Volumes of functionally defined posterior and anterior basal forebrain sub-regions were extracted using an established automated MRI volumetry approach based on a stereotactic atlas of cholinergic basal forebrain nuclei. As a specificity analysis, hippocampal volume was added to the analysis. A reduction in posterior basal forebrain volume was found in the hypo-cholinergic as compared to both normo-cholinergic PD and control participants, whereas for the anterior basal forebrain the evidence was inconclusive. In continuous association analyses, posterior basal forebrain volume was significantly associated with cortical PMP PET signal in a temporo-posterior distribution. It was noted that those participants who were categorized as hypo-cholinergic based on cortical PMP binding showed evidence for degeneration of the posterior basal forebrain not only as compared to controls, but also in comparison to the normo-cholinergic Parkinson's disease group. The combined models for the prediction of cognitive scores showed that both cholinergic markers (posterior basal forebrain volume and cortical PMP PET signal) were independently related to multi-domain cognitive deficits, and were more important predictors for all cognitive scores, including memory scores, than hippocampal volume.

Overall, it was concluded that degeneration of the posterior basal forebrain in Parkinson's disease is accompanied by functional cortical changes in acetylcholinesterase activity, and that both PET and MRI cholinergic imaging markers are independently associated with multi-domain cognitive deficits in PD

without dementia. Comparatively, hippocampal atrophy seems to have minimal involvement in the development of early cognitive impairment in PD.

Schumacher J, Kanel P, Dyrba M, Storch A, Bohnen NI, Teipel S and Grothe MJ, Structural and molecular cholinergic imaging markers of cognitive decline in Parkinson's disease. *Brain* 2023; July5; awad226.

Safety and efficacy of venglustat in GBA1-associated Parkinson's disease: an international, multicentre, double-blind, randomized, placebo-controlled, phase 2 trial

Variants in the glucocerebrosidase A (GBA) gene affect Parkinson's disease risk and phenotypic manifestations. Since high level of glucosylceramide associated with low GBA1 activity are associated with worsened clinical manifestations of PD, amelioration of elevated glucosylceramide might be expected to improve PD. In this manuscript the MOVES-PD investigators used assessed safety, efficacy, and target engagement of the glucosyceramide synthase inhibitor, venglustat, in early PD (Hoehn and Yahr $\leq$ 2) associated with GBA1 variants. This was a randomized, double-blind, placebo-controlled phase 2 trial Subjects were assigned to venglustat (110) or placebo (111). Outcome was assessed as change (baseline to 52 weeks) in the MDS-UPDRS parts II and III combined score. Despite lowering glucosylceramide by 75% in CSF and plasma, venglustat worsened part II + III score by 7.3 (SE 1.4) in PD vs placebo 4.7 (SE 1.3); however, this difference was not significant.

The authors posit multiple explanations for failure of venglustat to ameliorate PD symptoms, including antidopaminergic effects of the drug and inadequacy of the outcome measure. Alternatively, the hypothesis of elevated glucosylceramide causing PD in GBA1 variant carriers must be rejected. Further work will be necessary to resolve these issues.

Giladi N, Alcalay RN, Cutter G, et al. Safety and efficacy of venglustat in GBA1-associated Parkinson's disease: an international, multicentre, double-bind, randomized, placebo-controlled, phase 2 trial. *Lancet Neurol* 2023: 22: 8: 661-671.

IPX203 vs immediate-release carbidopa-levodopa for the treatment of motor fluctuations in Parkinson disease: The RISE-PD randomized clinical trial

Levodopa (LD) is the most effective oral therapy for the symptomatic treatment of Parkinson's disease (PD). Its use is complicated by the development of motor complications. It is hypothesized that motor complications may be due to short plasma half life of immediate release (IR) LD, variable absorption due to gastrointestinal dysmotility, and changes within striatal pathways. Well tolerated oral therapies with rapid symptomatic relief but longer plasma half life are needed. IPX203, a new oral extended-release carbidopa-levodopa capsule, was developed to address the short plasma half-life and limited absorption window for LD. IPX203 contains IR granules and extended-release coated beads. RISE-PD was a 20-week, randomized, double-blind, double-dummy, active-controlled, phase 3 clinical trial. Patients with PD taking a total daily dose of 400 mg or more of levodopa and experiencing an average of 2.5 hours or more daily off-time were included in the study. A total of 770 patients were screened, 140 were excluded (those taking controlled-release carbidopa-levodopa apart from a single daily bedtime dose, Rytary (Amneal Pharmaceuticals), additional carbidopa or benserazide, or catechol O-methyl transferase inhibitors or who had a history of psychosis within the past 10 years), and 630 were

enrolled in the trial. Following open-label immediate-release carbidopa-levodopa dose adjustment (3 weeks) and conversion to IPX203 (4 weeks), patients were randomized in a 1:1 ratio to double-blind, double-dummy treatment with immediate-release carbidopa-levodopa or IPX203 for 13 weeks. The primary end point was mean change in daily good on-time (i.e., on-time without troublesome dyskinesia) from baseline to the end of the double-blind treatment period. A total of 630 patients (mean [SD] age, 66.5 [8.95] years; 396 [62.9%] men) were enrolled, and 506 patients were randomly assigned to receive IPX203 (n = 256) or immediate-release carbidopa-levodopa (n = 250). The study met its primary end point, demonstrating statistically significant improvement in daily good on-time for IPX203 as compared to immediate-release carbidopa-levodopa (least squares mean, 0.53 hours; 95% CI, 0.09-0.97; $P = .02$), with IPX203 dosed a mean 3 times per day vs 5 times per day for immediate-release carbidopa-levodopa. Good on-time per dose increased by 1.55 hours with IPX203 compared to immediate-release carbidopa-levodopa (95% CI, 1.37-1.73; $P < .001$). IPX203 was well tolerated. The most common adverse events in the double-blind phase (IPX203 vs immediate-release carbidopa-levodopa) were nausea (4.3% vs 0.8%) and anxiety (2.7% vs 0.0%). In this study, IPX203 provided more hours of good on-time per day than immediate-release carbidopa-levodopa, even as IPX203 was dosed less frequently.

Hauser RA, Espay AJ, Ellenbogen AL, et al. IPX203 vs Immediate-Release Carbidopa-Levodopa for the Treatment of Motor Fluctuations in Parkinson Disease: The RISE-PD Randomized Clinical Trial. *JAMA Neurol.* Published online August 14, 2023. doi:10.1001/jamaneurol.2023.2679

Committee Activities

Clinical Care Committee

- **Rotation of Committee Chair:** Leadership for the clinical care committee rotates amongst the PADRECCs. The West LA PADRECC leads the committee for September/October. 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 treatment strategies, new medications and other procedures, and other clinical issues to improve patient care and outcomes across the national PADRECCs service area. It also serves to provide clinical support to the consortium network by focusing on procedures and measures to standardize clinical care across the PADRECC network.
- Recent agenda items have included:
    1. Future planning to enhance clinical service provision at PADRECCs : Suggestions and Strategies
    2. Discussion of new therapies in the pipeline and possible use in the VA in the future
    3. Discussion of DBS management and surgical programs at the PADRECCs
    4. Role of MRI guided focused ultrasound thalamotomy in the management of essential tremor and Parkinson's disease
    5. Exploring integration of VA Mind Brain Program for treatment of functional movement disorders into PADRECC clinical services

6. Exploring integration of CBT for Depression in PD into PADRECC clinical services- collaboration with the Mental Health Research and Program Development team at VA NJHCS

Education Committee

- **PADRECC/EES Movement Disorder Series-Webinars:** knowledge-based webinars to provide VHA healthcare professionals with current practice standards and emerging trends in the treatment of Parkinson's disease and other movement disorders. CEs are typically provided for the live webinars. Check out the following link for a list of past webinars and if you are interested in receiving a recording of a past webinar please email Gretchen.glenn@va.gov and list the date/topic of interest: https://www.parkinsons.va.gov/Consortium/Presentations/Audio_Conference/MDS.asp
  - **REGISTRATION NOW OPEN** - **Movement Disorders Series Part IV-Webinar- PD Rehabilitation** – October 19th, 2023 12pm – 4pm EST

- **National VA PD Newsletter**- View here!
- **Parkinson's Disease Rehab-Community of Practice/Microsoft Teams**- collaborating with rehabilitation subject matter experts across the VA with interest in PD to develop this COP to address and enhance rehabilitation care for Veterans with PD and similar conditions. The goal of the platform is to share evidence-based knowledge to inform PD-specific rehabilitation practices, provide access to up-to-date resources, program success and opportunities for improvement.
- **National Website Maintenance:** The committee performs periodic 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:**
  - **Patient Education Brochures-** https://www.parkinsons.va.gov/patients.asp
    - Exercise and Physical Activity
    - Motor Symptoms
    - Non-Motor Symptoms
    - Agent Orange and Toxic Exposures and PD
    - Fall Prevention
  - **PADRECC Support/Education Groups:** The PADRECCs are now holding virtual groups open to Veterans and care partners interested in attending. Please check out the National Website for listing of dates/times and contact person to register for the groups and please share with your patients/care partners: https://www.parkinsons.va.gov/patients.asp
  - **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**

- **Digital version:** https://www.parkinsons.va.gov/patients.asp
- **Printer friendly version:**

Suggested Edcuation Essentials