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THE TRANSMITTER

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Article Reviews

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Involvement of the Nigrostriatal Pathway in Patients With Idiopathic Normal Pressure Hydrocephalus and Parkinsonism

Idiopathic Normal Pressure Hydrocephalus is a challenging diagnosis with overlap of symptoms with conditions and often coexistence with other neurodegenerative disorders. One such common feature in iNPH is bradykinesia, which has overlap with parkinsonism and Parkinson's disease. DAT-SPECT is often used to assess presynatic nigrostriatal terminals to help to aid in diagnosis and nigrosome MRI may be complementary in identifying nigral cell body counts. This study aimed to characterize nigrostriatal contributions to parkinsonism in patient;s with iNPH through visualizing both striatal nerve terminals with DAT-SPECT and nigral cell bodies with 3T MRI. In a prospective study design, patients were recruited from one Movement Disorders specialty clinic at Santa Chiara Hospital at Pisa University between 2021 and 2023, with patients meeting diagnostic criteria for probable iNPH proposed by the Japanese Society of Normal Pressure Hydrocephalus 2021 criteria, parkinsonism according to the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria, and there ability to undergo both imaging modalities. 20 patients with iNPH and 20 patients with PD were included in the study. The two groups were comparable regarding sex, age, motor performance, and levodopa equivalent daily dose, however it was noted those with iNPH had a longer disease duration and lower cognitive scores. Among the patients with iNPH included in the study, 45% exhibited reduced striatal DAT binding while none showed nigrosome loss on MRI. All 20 patients with PD demonstrated reduced striatal DAT binding ($p < 0.001$) and nigrosome loss on MRI ($p < 0.001$). When comparing, after adjusting for age and sex, patients with iNPH exhibited significantly higher putaminal and caudate DAT binding than patients with PD. A subanalysis of patients with iNPH based on DAT-SPECT positivity revealed that those with abnormal dopaminergic imaging had a significantly higher MDS-UPDRS III score compared to those with negative DAT-SPECT. Their findings suggest that parkinsonian signs in iNPH correlate with reduced dopaminergic striatal terminals (as observed in DAT-SPECT), but significant nigral cell degeneration was not evident. In addition they identify a correlation between striatal DAT loss and motor impairment as assessed by the MDS-UPDRS III while no such correlation

was observed with the motor scores from the iNPH Rating Scale. They suggest that then in iNPH, striatal DAT binding may instead indicate axonal dysfunction due to a stretch injury caused by the force exerted on the lateral ventricle walls, rather than the actual number of viable neurons, or that a possible alternative hypothesis is that the abnormal dopaminergic imaging in iNPH stems from compensatory DAT downregulation. Limitations include the possibility that abnormal DAT-SPECT findings in patients with iNPH reflect underlying nigrostriatal degeneration not detected by MRI and can not exclude the potential for subsequent loss of nigral neurons in the iNPH patients. Additionally the small sample size and lack of pathology data limit the generalizability of these findings, especially in a diagnosis of iNPH, and that all patients, both iNPH and PD groups, were on dopaminergic therapy during DAT-SPECT imaging. Overall they conclude that their findings provide additional support for the hypothesis that striatal dopaminergic dysfunction may contribute to parkinsonism in patients with iNPH, along with the preserved intergrity of the nigrosome suggesting a mechanical disruption of the nigrostriatal pathway.

G. Palermo et al., Involvement of the Nigrostriatal Pathway in Patients With Idiopathic Normal Pressure Hydrocephalus and Parkinsonism *Neurology* First published online February 10, 2025

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Teleneurorehabilitation and Motor and Nonmotor Symptoms and Quality of Life in Parkinson Disease: The TELEPARK Randomized Clinical Trial

This was a single-center, randomized clinical trial which sought to evaluate the effectiveness and safety of tele-neurorehabilitation (TNR) in patients with Parkinson's Disease (PD) during the COVID-19 pandemic, particularly in low- and middle-income countries. The study aimed to determine if a tele-neurorehabilitation program, delivered via video calls, could improve motor and nonmotor symptoms and quality of life (QoL) in comparison to in-person rehabilitation. The study enrolled 63 participants (28 in person, 35 TNR) between September 2020 and July 2021. Both groups underwent a program involving physiotherapy, aerobic, and breathing exercises; however, the TNR group received most sessions via video calls after an initial in-person session. Primary outcome was the change in MDS-UPDRS score. Primary outcome measures revealed significant improvement in both TNR and in person groups (TNR: −6.74 vs in-person: −7.54) with no significant difference between them (P=0.39). The study also assessed secondary outcomes, such as the Non-Motor Symptom Scale (NMSS) and Parkinson’s Disease Questionnaire-8 Summary Index (PDQ8-SI), with both groups showing similar improvements. Taken together, this suggests non-inferiority of TNR vs in-person rehab. Rehabilitation programs are an important component to maintaining both motor and non-motor functioning in Parkinson’s Disease. This study may be helpful to keep in mind when taking care of individuals in rural areas or underserved populations who do not have the means to travel for in person rehabilitation programs. Further studies with larger samples and longer follow-up are necessary to confirm the long-term benefits of TNR, and the feasibility of expanding this approach globally remains to be explored.

Rajinder K. Dhamija, FRACP, Alvee Saluja, DM, Divyani Garg, DM, et al. Published in JAMA Neurol. February 24, 2025. doi:10.1001/jamaneurol.2024.5387

Mesdopetam for the Treatment of Levodopa Induced Dyskinesia in Parkinson's Disease: A Randomized Phase 2b Trial

Elevated levels of D3 receptors have been seen in the dorsal striatum of levodopa treated mouse models. It is hypothesized that it is involved in levodopa-induced dyskinesia (LID) through its interactions with D1 receptors. D3R knockout mice have decreased LID compared to wild-type and had no decrease in the motor benefits of levodopa. Similar effects on LID were seen with D3R antagonism in the same study. 1

Mesdopetam is a a dopamine D3 receptor antagonist. This was a Phase 2b randomized controlled trial aimed to assess its efficacy and safety in treating LID in Parkinson's disease (PD). Patients with ≥2 hours of troublesome dyskinesia were assigned to receive placebo or mesdopetam at doses of 2.5 mg, 5 mg, and 7.5 mg twice daily for 12 weeks. The primary endpoint was the change in ON time without troublesome dyskinesia, measured using home diaries. Secondary endpoints focusing on dyskinesia severity were measured using the modified UDysRS and MDS-UPDRS Part 4.2.

Although mesdopetam did not significantly improve Good ON-time compared to placebo, it demonstrated clinically meaningful improvements in secondary outcomes, particularly the modified UDysRS for the 2.5 mg and 7.5 mg doses. The decrease for the 7.5mg group was 12 points. A meaningful clinical decrease is 8. Additionally, the 7.5 mg dose was associated with a significant reduction in OFF time, showing dose-dependent efficacy. The adverse event profile was similar to that of placebo.

In conclusion, despite failing to improve Good ON-time, mesdopetam showed potential in reducing dyskinesia symptoms, particularly at the 7.5 mg dose, warranting further investigation. The study suggests that mesdopetam may provide an alternative treatment option for managing LID in PD, although larger studies are necessary to confirm its long-term benefits and optimal dosing regimen. 2

Citations:

1. Solís O, Garcia-Montes JR, González-Granillo A, Xu M, Moratalla R. Dopamine D3 Receptor Modulates l-DOPA-Induced Dyskinesia by Targeting D1 Receptor-Mediated Striatal Signaling. Cereb Cortex. 2017 Jan 1;27(1):435-446. doi: 10.1093/cercor/bhv231. PMID: 26483399; PMCID: PMC5939228.
2. Antonini, A., O'Suilleabhain, P., Stocchi, F., Landström, J., Waters, S., Sonesson, C. and Tedroff, J. (2025), Mesdopetam for the Treatment of Levodopa Induced Dyskinesia in Parkinson's Disease: A Randomized Phase 2b Trial. Mov Disord Clin Pract. https://doi.org/10.1002/mdc3.70004

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 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 PADRECC Associated Sites by focusing on procedures and measures to standardize clinical care across the PADRECC network.
- **Recent agenda items have included:**

1. **Skin biopsy for alpha-synuclein - Syn-One** (CNS life sciences): practice and protocol use in the PADRECCs
2. **Movement disorders surgical procedures:** Focused Ultrasound Thalamotomy and Gamma Knife Thalamotomy- PADRECC outcomes
3. **Parkinson's KinetiGraph (PKG):** practice and protocol use in the PADRECCs
4. **Vyalev:** subcutaneous continuous infusion therapy - practice and protocol use in the PADRECCs

Education Committee

- **PADRECC/ILEAD 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 provided for the live webinars. Check out the following link for a list of past webinars: Movement Disorders Series - Parkinson's Disease Research, Education and Clinical Centers (va.gov)

14th PADRECC/MIRECC Symposium - Webinar

Parkinson's Disease Hot Topic Debates

March 28th, 2025 9am-1pm PST / 12pm-4pm EST

The Parkinson's Disease Research, Education & Clinical Centers / Mental Illness Research, Education & Clinical Centers (PADRECC / MIRECC) symposium has provided a dynamic educational opportunity for VA clinicians and clinical researchers for over 2 decades now. The purpose of this meeting is to continue the practice of delivering an informative symposium for clinicians and clinical researchers. The intersection of PADRECC and MIRECC focuses on neurodegenerative disorders, including Parkinson's disease, Alzheimer's disease and dementia with Lewy bodies, which are highly prevalent in the Veteran population and are projected to increase in prevalence in the VA and nationally as the population ages. This symposium will explore current controversies related to: (1) potential psychiatric risk factors for developing

Parkinson's disease; (2) the impact certain Parkinson's disease treatments have on psychiatric and cognitive symptoms; and (3) common treatment recommendations.

The **target audiences** for this program are physicians, nurses, psychologists, social workers, physical therapists, occupational therapists, speech therapists and other healthcare professionals providing care to patients with Parkinson's disease, dementia, and psychiatric disorders.

- **PD Hospital Safety Training Presentation:** developed a short grab and go presentation for VA CLC, CNH and Veteran State Home staff to improve the care of Veterans with PD who reside there. Committee is currently piloting locally.

- **The Parkinson's Foundation/VHA Partnership**: this committee serves as point of contact for partnership activities.
    - The **2024/2025 PF Veteran Webinar Series** is underway.
    - **PD GENEration Webinar:** Dr. James Beck of The Parkinson's Foundation is hosting a webinar for PADRECC & PAS providers on 3/21/25 to discuss study findings, ongoing genetics research and ways to support patients interested in genetic testing.
    - **VA Professionals Survey-** being developed to gain a sense of VA Clinicians' PD education needs/resources.

- **VA Annie Mobile App Protocol for PD:** exploring the development of a protocol that will be available nationwide to provide educational messages related to PD and will link to specific resources such as exercise videos, informational PDF and websites.

- **Parkinson's Disease Rehab-Community of Practice on Microsoft Teams**- collaboration 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. All are welcome to join: https://teams.microsoft.com/l/channel/19%3a_NAJNcVxoyd5XB0M_UnwK4Ym7vi8C971TC0xqerdfts1%40thread.tacv2/General?groupId=bf9f6fc8-06da-401e-99c5-6dd0b47494ee&tenantId=e95f1b23-abaf-45ee-821d-b7ab251ab3bf

- **PD 101 webinar**: This webinar for patients, care partners and anyone interested in learning more about Parkinson's disease and the PADRECC program is being held on **April 21, 2025**.

- **PADRECC Transmitter:** This committee continues to assemble and distribute this *e*-newsletter every other month.