identical to the Lamictal used in ANDA studies; other generic formulations, particularly oxcarbazepine and valproic acid, often provide concentration ratios near the 80% to 125% acceptance limits.[8] Third, disparate lamotrigine generic formulations (ones from the 35 manufacturers whose products' bioequivalence differed most from Lamictal) were not studied. The investigators were unable to obtain consistent batches of disparate generic lamotrigine products for their studies, and the differences between ANDA bioequivalence ratios and mean dissolution for the generic products they evaluated were less than 5%. Is it possible that AED products with bioequivalence ratios that are near the lower and upper acceptance bioequivalence ranges (80% and 125% for the 90% CI of the product ratios) would provide larger concentration shifts than those reported for the FDA-sponsored lamotrigine studies?

Clinicians can be reassured by these studies and may inform patients that generic AED formulations are safe copies of reference-listed drugs. The studies do not, however, explain common patient complaints of clinical problems after generic switches. Berg et al[5] and Privitera et al[6] suggest that clinical problems may mean some patients may be having negative placebo responses or may represent fluctuations in individual absorption and tolerability, which may be true. However, the studies probably also underestimate the number of patients who may have larger drug fluctuations (eg, 20%) and clinical problems.[8] The American Epilepsy Society recently endorsed the FDA-sponsored study findings[9] but recommended additional study of formulation effects, particularly for modified-release AED formulations.[10] The society also recommended that clinicians counsel patients on the use of generic formulations to ensure that patients are not surprised by cosmetic changes in tablets and that patients receive stable treatment with either immediate-release or modified-release formulations.

Clinicians can boost patients' confidence in trying generic AEDs by noting that 3 recent FDA-sponsored studies showed the products are bioequivalent with brand-name formulations and are safe. This reassurance might reduce "nocebo" responses in patients who are anxious about losing seizure control. In addition, clinicians should remain vigilant about the potential problems associated with formulation changes, particularly when prescribing the other AEDs not tested in these studies.

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Author Affiliation: Department of Neurology, Johns Hopkins University, Baltimore, Maryland.

Corresponding Author: Gregory L. Krauss, MD, Department of Neurology, Johns Hopkins University, Meyer 2-147, 600 N Wolfe St, Baltimore, MD 21287 (gkrauss@jhmi.edu).

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Dopaminergic Imaging and Prodromal Parkinson Disease
A Key Biomarker Arrives

Ronald B. Postuma, MD

In the last 2 decades, it has become increasingly clear that Parkinson disease (PD) has a measurable prodromal stage,[1,2] meaning there are early symptoms or signs of neurodegeneration but full parkinsonism has not yet developed. Prodromal PD is characterized by combined motor and nonmotor changes, but in most individuals, nonmotor manifestations start first. The duration of the prodromal stage varies but likely exceeds 10 years in many. Diagnosing prodromal PD will become essential to develop and eventually use neuroprotective therapies. A neuroprotective therapy given in the clinical PD phase, although obviously useful in slowing further disability progression, cannot change the fact that much irreversible neurodegeneration has already occurred. On the other hand, if the same therapy is provided earlier during prodromal stages, it could potentially prevent clinical PD from developing at all.

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Recognition of this fact has led to enormous efforts to find ways of detecting prodromal PD. Many markers have been discovered,[1,2] which vary considerably in the level of evidence and, most notably, in predictive power. Relative risks range from 1.5 (depression) to more than 50 (idiopathic rapid eye movement sleep behavior disorder [RBD]).

Nonmotor markers predict PD because neurodegeneration usually starts outside of the motor substantia nigra.[3] However, once PD spreads to the substantia nigra, it still takes time before full parkinsonism can be diagnosed. This is because basal ganglia systems have redundancy; mild dopaminergic denervation can be tolerated without bradykinesia or rigidity (and even after they start, they can be initially difficult to define reliably). This early dopaminergic denervation should be measurable. However, most of the direct evidence for this comes from studies using clinical motor testing, in which patients destined to develop parkinsonism show measurable motor abnormalities 5 to 8 years before diagnosis.[4,5]

For decades, it has been possible to measure dopaminergic innervation from the substantia nigra to the striatum using positron emission tomography (PET) and single-photon emission computerized tomography (SPECT). Normal dopaminergic PET/SPECT scans are a strong sign against true neurodegenerative parkinsonism[6]; it is an exclusion criterion from probable PD diagnosis in the International Parkinson and Movement Disorder Society Clinical PD diagnostic criteria.[7] (Note that dopaminergic PET/SPECT scan cannot diagnose PD as the cause of parkinsonism because it is also abnormal in other parkinsonian conditions.) Generally, by the time someone is diagnosed with clinical PD, dopaminergic scans document a 30% to 60% loss; it seems logical that milder degrees of loss should be present earlier.

Despite this rather obvious hypothesis, there has been minimal direct evidence that dopaminergic PET/SPECT scans predicts disease. To my knowledge, the only published studies are a small study[8] in which 2 of 4 family members of patients with PD with olfactory loss (hyposmia) and abnormal dopamine SPECT findings developed PD over 2 years and a second study[9] from a population of patients with idiopathic RBD in which 6 of 8 patients who developed PD or cognitive loss had abnormal SPECT findings 21 months before developing PD (compared with 11 of 35 [31%] who remained disease-free). There have been no large general population studies documenting predictive value of dopaminergic PET/SPECT scans.

In this issue of *JAMA Neurology*, Jennings et al[10] describe the eagerly awaited Parkinson Associated Risk Study (PARS) results. This study aimed to test to what degree dopamine transporter (DAT) SPECT could predict PD and other neurodegenerative synucleinopathies. The investigators used a 2-step strategy to minimize the number of DAT scans performed, starting with olfactory testing. Olfaction is a very well-established predictor of PD, with relative risks that approximate 4 to 5.[1] Patients with hyposmia (and some control patients with normal olfaction) underwent DAT scanning to detect dopaminergic denervation. Among 152 hyposmic patients scanned and observed for 4 years, 21 (13.8%) had abnormal scan results, 109 (71.7%) had normal scan results, and 22 (14.5%) had borderline scan results. Over 4 years, 14 of 21 (67%) of those with abnormal scan findings converted to PD compared with only 3 of 109 (2.8%) with normal scan findings. This clearly establishes that DAT-SPECT can predict PD.

A few points deserve emphasis. Although it should surprise few that DAT-SPECT can predict PD, it was unclear how reliable or specific it might be. In this case, the relative risk for those with abnormal scan findings compared with those in the clearly normal range is approximately 24 (excluding borderline scan findings). This relative risk drops to 17 if borderline scan findings are included as normal scans and to 13.5 if they are included as abnormal. This makes DAT scanning now the second most powerful known predictor of PD, second only to polysomnography-proven RBD.[1] Based on this study, in the new International Parkinson and Movement Disorder Society prodromal criteria, abnormal DAT-SPECT results would provide a positive likelihood ratio for prodromal PD of approximately 80.[1] (Note the published prodromal criteria used estimates from the PARS abstract, but this final publication has different values.)

Second, this study focused on people with hyposmia (only 26 normosmic individuals were observed over the study period), and the predictive value may be different in those with normal olfaction. Although there is no way to know if the relative risk would be higher, lower, or the same, the fact that normosmic individuals have lower baseline risk would imply that the absolute risk of PD with abnormal DAT-SPECT scan findings would be lower in a population that includes normosmic individuals.

Third, the estimate of amount of change in DAT binding over the course of the study may be extremely useful in planning clinical trials. A trial of neuroprotective therapy in prodromal PD will eventually happen (hopefully sooner rather than later), and in such a trial, it would be strongly preferable to have a biomarker of change. This would help validate findings of a positive clinical outcome (eg, phenoconversion to PD or dementia). Moreover, if sufficiently sensitive, it might also provide an early signal of benefit/futility to provide funders with the confidence to proceed with large and expensive phase 3 trials. In those patients with a clear DAT deficit at baseline, DAT binding decreased by 20% (SD, 15%) over the 4 years (ie, 5% per year). This is similar to the only other prodromal dopaminergic SPECT scan assessment in an RBD population, which found a 16% to 19% decline in putamen binding over 3 years.[11] Using simple sample size calculators, if a neuroprotective agent were to slow this by 50% (to 10% [SD, 15%]), it would require approximately 36 patients in each group in a 4-year trial to have 80% power to show a benefit (and, presumably, approximately 72 patients for a 2-year trial).

Fourth, we do not yet know how long the prodromal interval for DAT-SPECT is or, in other words, how long before PD diagnosis DAT-SPECT results become abnormal. However, the PARS study is continuing follow-up; once complete, the inflection point from normal can be directly estimated. Of note, patients who eventually converted to PD had higher baseline

Unified Parkinson's Disease Rating Scale scores (the primary clinical history/motor examination scale for PD); it should not be assumed that DAT-SPECT can detect abnormalities any earlier than clinical examination. However, based on observations in this and other populations,[4,5] DAT-SPECT should be able to do so more reliably.

Fifth, some other markers were assessed that also add useful information. Constipation could predict conversion with a relative risk of 2.8. A history of dream enactment behavior on a screening questionnaire (ie, possible REM sleep behavior disorder) was associated with a relative risk of 2.8 and depression had a relative risk of 2.4, although these 2 variables were not statistically significant. These estimates are generally consistent with the previous literature.[1,2,12]

Sixth, the type and nature of neurodegenerative disease conversion is notable. Surprisingly, only 1 participant with a DAT deficit developed a primary dementia syndrome; the remainder all developed PD first. This is unexpected because primary dementia with Lewy bodies (that starts with dementia rather than parkinsonism) is approximately as common as PD and is also associated with early DAT scan abnormalities. Three convertors did not have a DAT deficit at baseline; all had action tremor with bradykinesia, and 2 of these patients had no rigidity. Bradykinesia assessment can be difficult in the presence of action tremor, so it is possible that the diagnosis was incorrect in these patients. If so, the diagnostic utility of DAT scanning would actually be better than estimated. Note also that 2 convertors to PD did not have bradykinesia on examination; bradykinesia is generally considered an essential part of diagnosis of PD,[7,13] and so their inclusion as convertors is controversial.

So where will the field move now? It is clear that dopaminergic functional imaging will become a key part of the future of prodromal PD. It will likely be included in any future neuroprotective trial, both to ensure patients truly have prodromal PD and as a quantitative biomarker of change. And once neuroprotective therapy becomes available, it may become an integral part of the programs we will develop to find patients with prodromal PD. Given its expense, it is presumably likely to be used as a secondary screen for persons who screen positive on simpler but less specific measures, perhaps along with other highly specific secondary markers, like polysomnography-proven RBD or perhaps even tissue biopsy.[14]

To conclude, the investigators are to be congratulated for the successful conclusion of a long and arduous journey. The field of prodromal PD is expanding exponentially, and the PARS study becomes one of its pillars.

ARTICLE INFORMATION

Author Affiliation: Department of Neurology, McGill University, Montreal General Hospital, Montreal, Quebec, Canada.

Corresponding Author: Ron B. Postuma, MD, Department of Neurology, McGill University, Montreal General Hospital, 1650 Cedar Ave, Montreal, QC H3G1A4, Canada (ron.postuma@mcgill.ca).

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